

PERFECT STROKE

*PERformance, Effectiveness, and Costs
of Treatment episodes in Stroke*

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ACADEMIC DISSERTATION

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To my family

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals:

- I Meretoja A, Roine RO, Kaste M, Linna M, Juntunen M, Erilä T, Hillbom M, Marttila R, Rissanen A, Sivenius J, Häkkinen U. Stroke Monitoring on National Level. PERFECT Stroke, a Comprehensive Registry-Linkage Stroke Database in Finland. *Stroke*. 2010;41(10):2239-2246.
- II Meretoja A, Kaste M, Roine RO, Juntunen M, Linna M, Hillbom M, Marttila R, Erilä T, Rissanen A, Sivenius J, Häkkinen U. Trends in treatment and outcome of stroke patients in Finland from 1999 to 2007. PERFECT Stroke, a nationwide register study. *Ann Med*. 2011;43(S1):S22-S30.
- III Meretoja A, Roine RO, Kaste M, Linna M, Roine S, Juntunen M, Erilä T, Hillbom M, Marttila R, Rissanen A, Sivenius J, Häkkinen U. Effectiveness of Primary and Comprehensive Stroke Centers. PERFECT Stroke: A Nationwide Observational Study. *Stroke*. 2010;41(6):1102-1107.
- IV Meretoja A, Kaste M, Roine RO, Juntunen M, Linna M, Hillbom M, Marttila R, Erilä T, Rissanen A, Sivenius J, Häkkinen U. Direct Costs of Patients With Stroke Can Be Continuously Monitored on a National Level. Performance, Effectiveness, and Costs of Treatment Episodes in Stroke (PERFECT Stroke) Database in Finland. *Stroke*. 2011;42(7):2007-2012.

In addition, some unpublished data are presented.

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ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical Classification System
BAC	Brain Attack Coalition
CHESS	Centre for Health and Social Economics
CDR	Causes of Death Registry
CI	Confidence Interval
CSC	Comprehensive Stroke Center
CSF	Cerebrospinal Fluid
CT	Computer Tomography
CVT	Cerebral Venous Thrombosis
DALY	Disability Adjusted Life Years
DRG	Diagnosis Related Group
EUSI	European Stroke Initiative
GH	General Hospital
GZLM	Generalized Linear Model
HILMO	Finnish Hospital Discharge Register
HIV	Human Immunodeficiency Virus
HUCH	Helsinki University Central Hospital
HUS	Helsinki and Uusimaa Hospital District
ICD-9/10	International Classification of Diseases, 9 th / 10 th Version
ICH	Intracerebral Hemorrhage
ICP	intracranial Pressure
IQR	Interquartile Range
IS	Ischemic Stroke
KELA	<i>see SII</i>
KTL	National Public Health Institute
LOS	Length of Stay
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NNT	Number Needed to Treat
OECD	Organisation for Economic Co-operation and Development
PERFECT	PERFormance, Effectiveness, and Costs of Treatment episodes
PSC	Primary Stroke Center
SAH	Subarachnoid Hemorrhage
SII	Social Insurance Institute
SITS	Safe Implementation of Thrombolysis in Stroke study
SSCA	Scottish Stroke Care Audit
STAKES	National Research and Development Centre for Welfare and Health
THL	National Institute for Health and Welfare
WHO	World Health Organization

ABSTRACT

Stroke is a major cause of death and disability, incurs significant costs to healthcare systems, and inflicts severe burden to the whole society. There are numerous evidence-based interventions available for treatment of stroke patients, but these are not utilized optimally. Information on details of stroke care in Finland has been systematically gathered in several population-based epidemiological studies between 1967 and 1998, but not since. Feedback on quality and outcome of care is vital for improving daily clinical practice. In the PERFECT Stroke study presented here, a system for monitoring the Performance, Effectiveness, and Costs of Treatment episodes in Stroke was developed in Finland.

In this study, only first-in-a-lifetime stroke patients were included. Existing nationwide administrative registries were linked at individual patient level with personal identification numbers to depict whole episodes of care, from acute stroke, through rehabilitation, until the patients went home, were admitted to permanent institutional care, or died. Patient catchment was hospital-based, while data collection on follow-up was population-based. Several healthcare providers, multiple comorbidities, and need for long-term follow-up with secondary prevention interventions were usually involved in the care of patients, and all of these were evaluated from existing national databases. Data on national trends in the epidemiology, treatment, and outcome of stroke patients from the year 1999 to 2008 were gathered for the present study. For comparisons in time and between providers, patient case-mix was adjusted for.

The PERFECT Stroke database includes 104 899 first-ever stroke patients over the years 1999 to 2008, of whom 79.1% had ischemic stroke (IS), 13.6% intracerebral hemorrhage (ICH), and 7.3% subarachnoid hemorrhage (SAH) as their first-ever stroke. The median age was 74 years, with one in four patients being working-age, below 63 years of age. Of all patients, 6% were living in an institution before their first-in-a-lifetime stroke.

An age and sex adjusted decrease of 18% in the incidence of stroke was observed over the study period, 1.8% improvement annually. All-cause 1-year case-fatality rate of stroke patients improved from 28.6% to 24.6%, or 0.5% annually. Accordingly, the positive developments observed since the 1970's of decrease in both stroke incidence and case-fatality rates continued during the current study period. This can be explained by continuing favorable developments in stroke risk factors in the population, and with improved care. Due to improved survival, the expected median lifetime after stroke increased by 2 years for IS patients, being 7 years and 7 months at the end of the study period, and by 1 year for ICH patients, being 4 years 5 months. No change could be seen in median SAH patient survival, which was more than 10 years. Increased survival has led to increased stroke prevalence in the population, estimated to be 82 000 people, 1.5% of total population of Finland in 2008.

In this study, for the first time, modern stroke center care was shown to be effective at population level covering the whole nation, with significant decrease in both death and risk of institutional care in patients treated in stroke centers, number needed to treat to prevent these poor outcomes at one year from stroke 32; 95% confidence intervals 26 to 42.

Despite improvements over the study period, more than a third of Finnish stroke patients did not have access to this evidence-based stroke center care, and half of survivors did not receive secondary preventive medications as recommended in national guidelines. There is a pressing need to improve these clinical practices. Monitoring for such developments together with public awareness of the issues will hopefully promote change.

The mean direct healthcare cost of a stroke patient was shown to be about 20 000 € over the first year after stroke, and about 10 000 € annually thereafter for survivors. Only part of these costs were incurred by the stroke, as the healthcare of the same patients cost about 5000 € over the one year immediately before their initial stroke. The total costs of a stroke patient were estimated to be about 85 000 € over their remaining lifetime after their first-ever stroke. With the increased prevalence of stroke in the society, already 7% of all healthcare costs are used in the treatment of stroke patients, i.e. 1.1 Billion € annually.

Most of the results in this study are only applicable in Finland. For the international audience, there are two messages. 1) Stroke center care is effective, and should be made available for all stroke patients. 2) It is possible, in a suitable setting with high-quality administrative registries and a common identifier, to avoid the huge workload and associated costs of setting up a conventional stroke registry, and still be able to acquire a fairly comprehensive set of information on stroke care and outcome.

1 INTRODUCTION

Sometimes blood does not flow in the brain as it should do. It either stops; leaving neurons deprived of oxygen and glucose, or breaks outside of its vessels; tearing the soft brain tissue with force and pressure. In these situations, part of the brain dies, and we see a clinical syndrome known as a stroke.

As much as understanding on the mechanisms involved in these disturbances of blood flow has been gained, there is still scarce little we can do. Mostly, nature takes its course and eventually repairs part of the damage. We can try to clear the blockage in the flow, but in only few percentages of ischemic stroke patients this is attempted; and re-canalization of the occluded vessel succeeds in only half of these. In bleeds, a majority of the damage is done immediately. Thus, acute stroke care is mainly about helping the nature, giving the damaged brain an optimal environment to heal. We try to normalize and optimize brain physiology, although we know little of what would be optimal here. Irrespective of our attempts, eventually balance will be restored, dead tissue will be cleared away, and viable tissue will take over some of the lost functions. Lying in a bed, immobile, incapacitated, and under stress, is a state unnatural for the whole human body, leading to problems also outside of the brain. Many of them can be looked for, treated, and prevented. The factors that have caused the blood flow disruption, such as hypertension or arterial stenosis, usually do not go away by themselves, and often produce new attacks. To prevent this, several effective interventions are available. Helping the body to heal after stroke includes several concurrent and intertwined processes, best accomplished by a team of experts equipped with the appropriate tools and facilities. These things are what stroke care is all about.

It is only natural that professionals think they are good in their clinical work. However, this is not always true, and simple easily corrected issues can cause suboptimal results and even major complications. Medicine evolves, and not everybody is able to keep track while busy with the daily workload. National guidelines help, but are not always followed. Thus, quality needs to be measured; in order to pinpoint areas where practice fails to meet targets.

In the PERFECT Stroke study, an attempt has been made to measure the process of care of stroke patients in Finland, to depict the burden this disease inflicts on the society, to see whether anything is being done better, all of this to show us where we should try more.

2 REVIEW OF THE LITERATURE

2.1 Definition of Stroke

Voltaire (1694-1778) said: “If you wish to converse with me, define your terms.” Even today, among experts, the definition of the term stroke is far from uniform.

2.1.1 The WHO definition

Finland has a long tradition in the epidemiological research on stroke, and Finnish stroke experts have contributed to the most widely used definition of the disease over the last 40 years, the World Health Organization (WHO) definition.

The classical WHO definition of stroke was introduced with the WHO Collaborative Study on Cerebrovascular Disease in the Community. This first multinational epidemiological study on stroke was suggested in a WHO meeting in Monaco in 1970, where 51 stroke experts convened, among them two colleagues from our own institute, Rainer Fogelholm and Seppo Pakarinen. The meeting suggested a simple definition for stroke;

“A sudden onset of disturbance of focal brain function due to the blockage or rupture of blood vessels.” (WHO 1971)

The details of the study were planned in 1971, and 3 of the 24 collaboration researchers were Finns; Kari Aho (Helsinki), Pekka Puska (Kuopio), and Kalervo Salmi (Joensuu). Around the same time, Pekka Puska became the primary investigator of another epidemiological study on cardiovascular disease, the North Karelia project, initially planned in a seminar in September 1971 (*Puska et al. 2009*). The two studies have benefited from each other and contributed to a strong tradition of cardiovascular epidemiological research in Finland.

The WHO definition was originally formulated over several planning meetings, described in detail in three WHO internal documents not widely available:

- WHO: Control of stroke and hypertension in the community, Report of a WHO meeting, Geneva, February 1971. Internal Document CVD/71.3, Geneva, WHO, 1971
- WHO: Community control of stroke and hypertension. Report of a WHO meeting, Goteborg, November-December 1971. Internal Document CVD/72.1, Geneva, WHO, 1972
- WHO: Control of stroke in the community. Methodological considerations and protocol of WHO stroke register. Internal Document CVD/S/73.6, Geneva, WHO, 1973

As these WHO internal documents are hard to come by, an often cited reference of the WHO definition is the one described in the WHO Chronicles by Hatano (*Hatano 1972*):

Stroke was regarded by the meeting as being manifested by rapidly developing clinical signs of focal or global disturbance of cerebral function leading to death or lasting more than 24 hours with no apparent cause other than a vascular one. Thus, the term covers patients presenting clinical signs and symptoms suggestive of subarachnoid haemorrhage, intracerebral haemorrhage, or cerebral ischaemic necrosis and also some patients in deep coma. It does not cover those with systemic circulatory failure or hypertensive encephalopathy.

The clinical diagnosis of stroke is used as the criterion for entry in the stroke register. Autopsied patients with fresh cerebrovascular disease who did not manifest clinical signs of stroke while alive are therefore not registered.

Transient cerebral ischemia is not included, since the scrutiny of patients in the community is limited and there is as yet no agreement on uniform diagnostic procedures for this condition. Chronic brain conditions with mental deterioration and gradually developing neurological abnormalities are also excluded from the study, since a vascular origin cannot be definitely proved and the management of patients suffering from these conditions differ from that of acute stroke patients.

Reports from the WHO Collaborative study have since quoted the definition with slight but not insignificant variations (underlined).

First scientific report from a population of the study (*Aho and Fogelholm 1974*):

Stroke is defined as rapidly developed clinical signs of focal (or global) disturbance of cerebral functions lasting more than 24 hours or leading to death, with no apparent cause other than a vascular origin. Included are subarachnoid hemorrhage, intracerebral hemorrhage and ischemic brain infarction, both embolic and nonembolic. Transient ischemic attacks are excluded according to this definition.

A preliminary report of the study results is another source that is often quoted as the WHO definition (*Hatano 1976*):

A stroke was defined as rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin. The term "global" is applied to patients in deep coma and to those with subarachnoid haemorrhage. Transient episodes of cerebral ischaemia were excluded by definition. Cerebrovascular lesions discovered at autopsy without having shown clinical manifestations in life were not registered as stroke.

The final report of the study again quoted a slightly different definition (Aho et al. 1980):

Stroke was defined as “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin”. This definition obviously includes most cases of subarachnoid haemorrhage, intracranial haemorrhage, and cerebral infarction, but not cases of transient ischaemic attacks. The term “global” disturbances of cerebral function refers only to patients with subarachnoid haemorrhage without focal neurological deficits.

It could therefore be argued, that the WHO definition is not quite uniform, but rather depends on the article quoted. In any case, the definition is a clinical one, reflecting the era before widespread use of computer tomography (CT) imaging of the brain.

Later, in the 1970's, the WHO provided some new definitions of cerebrovascular diseases, which still considered symptoms lasting less than 24 hours as TIA, but rather than define stroke, called symptoms lasting 1 to 21 days “reversible ischemic neurological deficit (RIND)”, and any symptoms lasting longer as “permanent prolonged neurological deficit (commonly known as “completed stroke”)” (WHO 1978) based largely on a previous US report (Millikan et al. 1975). In the 1980's, the WHO provided a new definition (Goldstein et al. 1989):

Clinically, a stroke is defined as an acute neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain. Excluded from this definition are syncope of cardiac or other origin in which no focal cerebral symptoms are present and uncomplicated SAH in which there is no damage to the brain itself. ... If the symptoms and signs disappear completely within a few minutes or hours (<24 hours by convention), the event is termed a TIA. ... Strokes can be divided into two broad categories according to the nature of the cerebral lesion: infarcts and hemorrhages. A cerebral infarct is the result of temporary or permanent occlusion of a feeding artery, extracranially or intracranially, or (more rarely) of venous thrombosis. A spontaneous cerebral hemorrhage is due to the rupture of an abnormal artery (aneurysm or AVM) or arteriole in the brain parenchyma.

The revised WHO definitions have not gained much attention, and the original definition is still most widely used.

2.1.2 International classification of diseases (ICD) definitions

Classification of diseases in Finland has been based on the WHO international classification of diseases, 8th version (ICD-8) over the years 1967-1986, 9th version (ICD-9) over the years 1987-1995, and 10th version (ICD-10) since 1996.

The classifications of 1967 and 1987 had significant national modifications. The Finnish ICD-9 had a fifth digit used for national purposes only. Within stroke diagnoses, the main difference as compared to the international version was the differentiation between patients with (fifth digit A) and without (X) infarction, used with the ICD-9 groups 433 and 434 (occlusion/stenosis of cerebral/pre-cerebral arteries). The discrepancy has been removed with ICD-10. Many countries still use the ICD-9. There are some differences in the logic of ICD-9 and ICD-10; with ischemic stroke (IS, 433-434 or I63 respectively) being classified into etiological subtypes differently in the two versions; ischemic stroke including venous thrombosis in ICD-10 (I63.6), but not ICD-9 (4376); and finally intracerebral hemorrhage (ICH, 431 or I63) and subarachnoid hemorrhage (SAH, 430 or I60) being subdivided by location in ICD-10, but not ICD-9.

2.1.3 Gray areas in the definitions

There are several cerebrovascular disorders on the border zone of the stroke definition, included in stroke by some, but not by others:

Subarachnoid hemorrhage (SAH)

From the WHO definition it is clear that SAH is considered a stroke, although many studies on stroke have excluded these patients, and rather included only ischemic stroke and primary intracerebral hemorrhages. SAH without damage to the brain is especially difficult to clearly include or exclude in stroke, as the existence or non-existence of brain damage is difficult to prove.

Epidural and subdural hematomas

Epidural and subdural hematomas are usually never considered a stroke when due to a trauma (ICD-10 codes S06.4 and S06.5), then being of traumatic origin, rather than of vascular origin. Epidural and subdural hematomas may develop without a known trauma, and are then coded as I62 in the ICD-10 system. Some epidemiological studies using ICD-classification have included these in the definition of stroke, while most experts would not consider subdural hematoma as "vascular cause" (*Albers et al. 2002*).

Traumatic ICH and SAH

Like traumatic epidural and subdural hematomas, trauma can also produce ICH or SAH (ICD-10 diagnoses S06.3 and S06.6 respectively). These are not usually considered stroke, although missing patient history may sometimes make it difficult to clinically differentiate between traumatic and non-traumatic intracranial hemorrhages.

Cerebral venous thrombosis (CVT)

CVT without brain damage should not be a stroke according to any definition, and is not considered one in the new ICD-10 classification (I67.6). Many stroke studies have excluded CVT also when it causes an infarct (ICD-10; I63.6) or a hemorrhage (no distinct ICD-10 code, included in I61), a legacy of the ICD-9 coding logic.

Hypoxic-ischemic encephalopathy

Global ischemia of the brain, as in cardiac arrest, is not considered stroke in the WHO definition (*Hatano 1972*), but some literature does count this as a special case of stroke.

Recanalization of ischemic stroke, and surgery of ICH

There is some discrepancy in coding of strokes when symptoms are reversed with therapy, such as thrombolytic therapy or mechanical thrombectomy in ischemic stroke, or surgery in hemorrhagic stroke.

Retinal ischemia

While transient blindness due to ischemia of the retina, i.e. amaurosis fugax, is in the ICD-10 classification considered within TIA (G45.3), permanent ischemia of the retina, "retinal stroke", is not classified within the stroke diagnoses (H34).

Ill-defined stroke

Patients with a clinical picture of stroke and no imaging available are often diagnosed as ill-defined or undetermined stroke. While purely clinical diagnosis of stroke is quite acceptable according to the WHO definition, in developed countries imaging is currently standard practice, perhaps omitted only in some elderly patients with a very poor prognosis. A review of the literature showed that with purely clinical diagnosis, 21% of patients considered as having a stroke truly have a different condition, and thus are given an incorrect stroke diagnosis. In addition, 14% of strokes are misdiagnosed as another condition, whereby the stroke is missed. Therefore no reliable distinction between ischemic and hemorrhagic stroke can be made purely on clinical grounds (*Goldstein and Simel 2005*).

2.1.4 New tissue-based definitions

With clear imaging and cerebrospinal fluid (CSF) findings, although subject to some error, the diagnoses of ICH (*Qureshi et al. 2009; Cordonnier et al. 2010*) and SAH (*van Gijn et al. 2007*) are rather straightforward. However, with ischemic stroke, the diagnosis has been traditionally more clinical, often with no imaging findings if imaged early and with CT technology. With better understanding of the disease mechanisms, and new imaging possibilities, proposals for revised diagnostic criteria for ischemic stroke have been put forward. The artificial time-based boundary between ischemic stroke and TIA, set in the

WHO definition at 24-hours of symptom duration, has been questioned with new tissue-based diagnostic criteria:

A TIA is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction. (Albers et al. 2002).

In the future, the definition of stroke will remain a clinical one, but imaging will be compulsory to rule out other explanations for the symptoms, and, in the case of resolved symptoms, to visualize subclinical stroke.

Definition of stroke

Summary points

1. Finnish physicians were involved in formulating the classic WHO definition of stroke in the 1970's.
2. The definitions are not quite uniform and may or may not include certain types of cerebrovascular diseases.
3. Although the definitions do not clearly state this, it has been customary to consider stroke as cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage, due to arterial or venous causes, and exclude TIA, hypoxic-ischemic encephalopathy, traumatic hemorrhages, and non-traumatic epidural and subdural hemorrhages.
4. Stroke diagnostic criteria have changed with enhanced imaging and better understanding of pathology. This will lead to increase in total stroke cases, as more cases are diagnosed as ischemic stroke, and fewer cases as TIA.

2.2 Incidence of Stroke

Incidence is the number of new (first-in-a-lifetime) stroke cases in a certain population and within a given period, usually one year. Incidence is often expressed as cases per 1000, 10 000, or 100 000 persons at risk, either in the whole population, in a certain age- and/or sex- group, or in an adjusted population. Adjusted populations are used to make incidence figures comparable in time or across populations. Several standard adjusted populations (Europe, World) exist for international comparison, while national comparisons are usually performed to a population of a fixed year.

International standards for stroke incidence studies have been suggested by Sudlow and Warlow (*Sudlow and Warlow 1996*). They suggest that hospital-based populations never represent the whole community, as a significant proportion of patients are not admitted to a hospital. Suggested reasons for not admitting are: death before admission; no perceived advantage due to old age, previous disability, too severe, or too mild stroke; too remote, expensive, not available, or full hospital. Population-based incidence studies with multiple overlapping case finding strategies are the golden standard of stroke incidence.

2.2.1 Worldwide incidence of stroke

The worldwide annual stroke incidence has been estimated at 9.0 million in the year 2004, of which 2.0 million occur in Europe (*WHO 2008*), and 0.6 in the USA (*Roger et al. 2010*). A recent systematic review on stroke incidence identified 56 population-based studies performed in 47 centers and 28 countries over the years 1970 to 2006 (*Feigin et al. 2009*). Only 12 countries have population-based data on time-trends in stroke incidence, namely Australia, Denmark, Estonia, Finland, France, Italy, Japan, New Zealand, Russia, Sweden, UK, and USA. The review revealed several worldwide trends:

- There has been huge differences in reported crude stroke incidence rates, ranging from 15 (Ibadan, Nigeria, years 1971-74) to 483 (Turku, Finland, year 1987) per 100 000 population.
- Age-standardized stroke incidence rates have declined by 42% since the 1970's in high-income countries (-1% annually), but increased by 125% in low to middle income countries (+5% annually).
- The same global trends in incidence can be seen in both young and elderly patients.
- In high-income countries, the reduction in incidence is more due to reduction in ICH than IS incidence, while there has been no change in SAH incidence.
- After adjusting for age, ischemic stroke is as common in high-income and low to middle income countries, but hemorrhagic stroke is twice as common in the low to middle income countries.

A separate systematic review has been performed for incidence of ICH (*van Asch et al. 2010*). This review did not analyze countries according to income, and while showing a 3% annual decrease in crude incidence of ICH, observed no change in age- and sex adjusted incidence among the studies with highest quality case-finding standards. Asian ethnicity was associated with two-fold incidence of ICH, and age was the strongest driver of incidence, with a ten-fold incidence among those aged 85+ when compared to the 50-year olds.

There is significant geographical variation as to stroke subtypes in the total stroke incidence. In addition to Asian race, also low-income countries tend to have a higher proportion of hemorrhagic strokes, possibly due to poor control of hypertension (*Feigin et al. 2009*). In the USA, 10% of all strokes are ICH, and 3% SAH (*Roger et al. 2010*), while in Japan the proportion of hemorrhagic strokes has been 20 to 30% (*Kubo et al. 2003; Yokota et al. 2004*), and even higher rates of 36% have been reported in Georgia (*Tsiskaridze et al. 2004*).

2.2.2 Incidence of stroke in Finland

Incidence of stroke in Finland has been studied in the academic dissertations of Seppo Pakarinen (*Pakarinen 1967*), Kari Aho (*Aho 1975*), Juhani Sivenius (*Sivenius 1982*), Mervi Kotila (*Kotila 1986*), Aimo Rissanen (*Rissanen 1992*), and Cinzia Sarti (*Sarti 1994*), and several other studies.

Helsinki subarachnoid hemorrhage study 1952-1961

Incidence of subarachnoid hemorrhage was studied by Seppo Pakarinen in the Helsinki area over the years 1952 to 1961. The study patients were hand-searched from the death certificates and hospital records of all hospitals in the Helsinki area. Altogether, 589 patients with primary subarachnoid hemorrhage were found, and 554 of these were incident cases. Crude incidence was 16 per 100 000 population (*Pakarinen 1967*). This study was the first population-based incidence study of SAH.

SII Mobile Clinic Health Examination Survey 1966-1976

The Social Insurance Institute Mobile Clinic Health Examination Survey (*Reunanen et al. 1983; Reunanen et al. 1986*) was a cohort follow-up study, with 12 cohorts of population aged above 15 years, distributed throughout Finland, recruited between 1966 – 1972, and a follow-up of mean 6 years, up to 1976. Several diseases were studied. Participation rate was 83% (n=24,747), and only 5% were lost to follow-up. In addition to clinical and questionnaire follow-up, the study used multiple registries to identify stroke incidence (death certificates, hospital discharge registries, invalidity pensions, and fully reimbursed chronic conditions). A total of 310 incident stroke cases were registered, and the crude annual incidence was 340 per 100 000 population, dropping to 275 annually if only properly ascertained cases were included. Two thirds of the cases were fatal, but an

autopsy was performed in only 19%. In half of the stroke patients, the stroke subtype could not be defined.

WHO Collaborative Study on Cerebrovascular disease in the community 1972-1974 and follow-up studies in the same regions

The first population-based incidence studies in Finland studying all stroke subtypes were conducted as part of the WHO collaboration in the areas of Espoo-Kauniainen and North Karelia. The Espoo-Kauniainen study started rapidly after the WHO planning meeting held in October 1971. The first announcement of the study was made in the Finnish Medical Journal in December 1971 (*Aho et al. 1971*), and the study ran for two years from January 1972 to December 1973. The detailed data on these patients were presented in the academic dissertation of Kari Aho (*Aho 1975*), and some further details of the same patients were presented in the dissertation of Mervi Kotila (*Kotila 1986*) and a later meta-analysis by Heikki Numminen and colleagues (*Numminen et al. 1996*). A total of 286 patients were included in the registry with multiple overlapping sources and hot pursuit of cases. Of these patients, 244 were first first-in-a-lifetime strokes while 42 (15%) had a history of stroke prior to 1972. The stroke subtypes were ischemic (61%), ICH (16%), SAH (15%), and undetermined (7%). Median age was 66 years, with a range from 24 to 93 years. In the very young population of the recently urbanized area, when only first-ever strokes were counted, the crude annual stroke incidence was 108 per 100 000 population. The results of the WHO study are summed in a preliminary report (*Hatano 1976*), and a final report (*Aho et al. 1980*), which confusingly report the numbers of patients in the Espoo-Kauniainen study to have been 299 and 303 respectively.

As part of Mervi Kotila's academic dissertation, a similar registry was kept in the same area for two years from April 1978 to March 1980. The methods were otherwise identical to those of the years 1972 to 1974, but outpatients were not searched for. In the 1972-1973 period, 12% of the patients in Aho's study were not admitted to a hospital (*Hatano 1976*). A total of 255 patients were included. Crude annual first-ever stroke incidence was 93 per 100 000 population, a 26% decrease from the previous period after age- and sex-standardization, but not statistically significant (*Kotila 1984; Kotila 1986*), and obviously partly explained by lack of outpatient pursuit.

The North Karelia study arm of the WHO study started in May 1972. As part of the WHO study, up to December 1974, it registered 938 stroke patients, about 85% of whom were incident cases, and 89% were treated in hospitals. Crude annual incidence was 171 per 100 000 population (*Puska et al. 1974; Hatano 1976; Aho et al. 1980*). Registration of stroke patients was continued in North Karelia for two decades, first as an independent registry, and then as part of the FINMONICA study over the years 1983 to 1992, but no quality control existed between 1975 and 1980, making the data for this period less comparable (*Tuomilehto et al. 1993*).

The incidence results of these WHO study and follow-up studies have been presented in several reports (*Aho and Fogelholm 1974; Puska et al. 1974; Aho 1975; Aho et al. 1976;*

Salonen et al. 1979; Aho et al. 1980; Kotila 1984; Kotila 1986; Tuomilehto et al. 1993; Numminen et al. 1996). It must be noted that the Espoo-Kauniainen 1972-1973 and the North Karelia studies registered also patients with a history of previous stroke, and these recurrent cases constituted 16% (*Aho and Fogelholm 1974*) and 20% of the incidence (*Puska et al. 1974*) respectively. There is some variation in the incidence reported from these studies, as recurrent cases are included in the incidence figures of some papers, and excluded from others.

Jyväskylä region 1976-1978 (SAH), 1985-1989 (ICH), 1985-86 and 1993 (All stroke)

Several studies on stroke epidemiology have been performed in the Jyväskylä region in Central Finland. The first project concerned SAH patients, and was run over the years 1976-1978, but was retrospective, and included only patients from hospital and autopsy records, $n=140$ incident cases. Crude incidence was 19 per 100 000 population (*Fogelholm 1981*). Total stroke incidence was studied more thoroughly in the Jyväskylä region over the periods of 1985-1986 ($n=219$), and 1993 ($n=189$), for one full year in both instances. In addition to hospital records and death certificates, also community health center data was collected. A CT scan or autopsy was performed in 68% of patients in the first period, and 91% of patients in the second period. Crude annual incidence decreased from 191 to 154 per 100 000 population. After age-standardization, a 28% decline in incidence was reported (*Fogelholm et al. 1997*). A similar method was used to gather information on ICH incidence over the years 1985-1989, $n=158$, and crude annual incidence was 31 per 100 000 (*Fogelholm et al. 1992*).

Kuopio region

As part of Juhani Sivenius's academic dissertation, a population-based stroke registry was kept in the Kuopio region (Kuopio, Maaninka, Siilinjärvi, Vehmersalmi) for 20 months, from 1st Oct 1978 to 31st May 1980, and 300 first-ever strokes were registered, together with 73 recurrent cases. Multiple overlapping casefinding strategies were utilized, and 40 cases were found from death certificates only. The annual crude incidence was 235 per 100 000 population (*Sivenius 1982*).

FINMONICA (1982-1992) and FINSTROKE (1993-1997) studies

The World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA) study was an international collaboration of uniform procedures to register cardiovascular disease and stroke (*Asplund et al. 1988; Tuomilehto et al. 1992; Thorvaldsen et al. 1995*). The study was run at three geographical areas in Finland (North Karelia, Kuopio, Turku-Loimaa) over the years 1983 – 1992, and in smaller areas of Kuopio and Turku over the years 1993-1997, with the names FINMONICA and FINSTROKE (*Tuomilehto et al. 1992; Sarti 1993; Sarti et al. 1993; Tuomilehto et al. 1993; Tuomilehto et al. 1996; Immonen-Raiha et al. 1997; Tolonen et al. 2002; Immonen-Raiha et al. 2003; Lehtonen et al. 2004; Sivenius et al. 2004; Sivenius et al. 2009*). The population-based study only included patients aged 25-74 ($n=5650$). In addition, patients aged >74 were registered in Turku from 1982 to 1992, and again from 1996 to 1998, and in Kuopio from 1990 to 1997 ($n=5493$) (*Lehtonen et al. 2004*). Multiple overlapping case-

finding strategies were used. CT, MRI, or autopsy rate approached 100% towards the end of the study. Even in the >75 year olds, only 2% of stroke cases were not imaged or autopsied, and a further 8% not imaged in the year 1997 (*Lehtonen et al. 2004*). Stroke incidence and mortality was reported to decline in Finland on average by 2.1% annually from 1982 to 1998 in the >74 year olds after age-standardization (*Lehtonen et al. 2004*), and by 1.9% annually from 1983 to 1997 in the <75 year olds after age-standardization (*Sivenius et al. 2004*).

Finnish Heart Association study 1989-1991

A study with the same methodology as the Espoo-Kauniainen studies was conducted over two year at four separate Finnish regions from August 1989 to August 1991. A total of 594 first-ever stroke patients were registered, and the crude incidence was 220 per 100 000 population. The study data has been published in comparison with the Espoo-Kauniainen studies. A 20% decrease in age-adjusted incidence from 1972 to 1991 was reported (*Numminen et al. 1996*) together with an observation of decrease in stroke severity (*Numminen et al. 2000a*).

CVDR

The Finnish Cardiovascular Disease Registry is a register-based database, available at www.ktl.fi/cvdr, joining the national hospital discharge registry (HILMO), and the causes of death registry (CDR) since year 1991 (*Laatikainen et al. 2004; Pajunen et al. 2005*). Stroke incidence was calculated with the ICD-9 diagnosis codes 430-432, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436, and the ICD-10 diagnosis codes I60-I64 excluding I63.6 (cerebral venous infarction), and thus included also non-traumatic epidural and subdural hematomas (I62). A stroke was considered incident when no prior stroke diagnoses were present for the previous 7 years. A declining trend in incidence was reported, over the years 1991 to 2002 and after age-standardization, to be about 2% annually (*Pajunen et al. 2005*). The total number of new annual stroke cases with this methodology has been 13 385 in 1991, 13 526 in 1999, and 13 374 in 2007 (*Laatikainen et al. 2004*).

Incidence of stroke

Summary points

1. Age-standardized incidence of stroke has declined over the last decades in high-income countries, especially in ICH patients, but also in IS patients.
2. Epidemiology of stroke in Finland has been well documented in several population-based studies over the last decades, up to year 1997, and in administrative register-based studies since.
3. Standardized stroke incidence has declined in Finland steadily since the 1960's.
4. The reduction in age-standardized incidence has counteracted the effects of the rapidly aging population, and the total number of stroke patients in Finland has been stable.

2.3 Risk Factors of Stroke

Advanced age is the most important risk factor for stroke, as stroke rates double for every 10 years of age after the age of 55 (*Goldstein et al. 2011*). The other non-modifiable risk factors are male sex, non-white race, and a family history of stroke (*Seshadri et al. 2010; Goldstein et al. 2011*). With a rapidly aging population in Finland, and no change in the other non-modifiable risk-factors, one would expect to see swiftly increasing numbers of stroke patients. This has not been the case, most likely attributable to positive developments in the modifiable risk factors of stroke.

Primary prevention is probably the most effective intervention against the burden stroke, but not easy to accomplish, and could be quite costly (*Kahn et al. 2008*). Prevention and treatment of hypertension is crucial in this aspect, together with healthy diet, physical activity, and campaigns against smoking / excessive alcohol use (*Salonen et al. 1982; Straus et al. 2002; Goldstein et al. 2006; Myint et al. 2009; Willey et al. 2009; Goldstein et al. 2011*). The recent INTERSTROKE study performed in 22 countries identified 5 risk factors which together accounted for 80% of the population-attributable-risk for stroke, namely hypertension, current smoking, abdominal obesity, poor diet, and lack of physical activity (*O'Donnell et al. 2010*). These risk factors were common for ischemic stroke and ICH.

Elevated **blood pressure** is a risk factor for all stroke subtypes (*Leppälä et al. 1999a*). Medical treatment of hypertension reduces the risk of ischemic stroke by 32% (*Goldstein et al. 2011*), and halves the risk of ICH (*Broderick et al. 2007*). Evidence on SAH risk reduction with treatment of blood pressure is lacking, although patients with treated blood pressure have a better prognosis after SAH (*Bederson et al. 2009*). Hypertension is the most important modifiable risk factor for both ischemic stroke and ICH, but its relative importance is larger in ICH (*O'Donnell et al. 2010*).

Smoking has been identified decades ago as a strong risk factor for SAH (OR 2.9; 95% CI 2.5-3.5), less so for ischemic stroke (OR 1.9; 1.7-2.2), while protection against ICH has been suggested in an earlier meta-analysis (OR 0.74; 0.56-0.98) (*Shinton and Beevers 1989*), but this was in the era before solid diagnostics with CT imaging. While the association of smoking risk with SAH and IS is rather proven (*Bederson et al. 2009*), also in Finland (*Fogelholm and Murros 1987; Juvela et al. 1993*), the evidence regarding smoking and the risk of ICH is more conflicting, with some studies showing an independent increased risk (*Kurth et al. 2003a; Kurth et al. 2003b; Broderick et al. 2007; O'Donnell et al. 2010*), while earlier studies performed in Finland did not show any association (*Fogelholm and Murros 1993; Juvela et al. 1995*), and a previous meta-analysis showed smoking to protect from ICH (*Shinton and Beevers 1989*). Smoking cessation reduces the risk of ischemic stroke by 50% in one year, and the risk from previous smoking disappears in 5 years after quitting cigarettes (*Goldstein et al. 2011*). Quitting smoking also reduces the risk of SAH (*Bederson et al. 2009*).

No clear association with elevated blood **cholesterol** and stroke mortality was found in a systematic meta-analysis, except for a subgroup of ischemic stroke patients younger than 60 years of age, and elevated cholesterol was inversely associated with mortality in the older age groups (*Lewington et al. 2007*). Lower mortality with higher cholesterol could be explained by less severe strokes in patients with high cholesterol (*Olsen et al. 2007*), and statins may play a role (*Elkind et al. 2005*). While higher cholesterol may produce more ischemic strokes, some studies have not confirmed this (*O'Donnell et al. 2010*), and there seems to be an inverse relationship in ICH patients, as higher cholesterol, and lower HDL cholesterol may protect from hemorrhagic stroke (*Tirschwell et al. 2004; O'Donnell et al. 2010*), especially in the older patients (*Lewington et al. 2007*). Overall, it seems that the relationship between cholesterol and stroke is not quite straightforward, with inverse relationships between cholesterol effect on ischemic and hemorrhagic stroke possibly counterbalancing each other (*Goldstein et al. 2011*).

While diabetes, cardiac disease, and systemic atherosclerosis are risk factors for ischemic stroke, their prevention coincides with the prevention of the stroke. Tight carotid artery stenosis is a special risk factor for stroke where medical prevention may be augmented with surgery in certain patients (*Brott et al. 2011*). **Atrial fibrillation** should be treated with anticoagulants when other risk factors of stroke are present (*Goldstein et al. 2011*). Scoring systems, such as CHADS₂ (*Gage et al. 2001*), or its improvements (*Lip et al. 2010a; Lip et al. 2010b*), may be used in deciding whether anticoagulation should be initiated. Although **diabetes** is a clear risk factor for all stroke subtypes (*Sarwar et al. 2010*), tight glycemic control does not reduce the risk of stroke once diabetes has developed (*Goldstein et al. 2006*). **Hormone replacement therapy** and **oral contraceptives** are risk factors for ischemic stroke, and should be stopped after a stroke or TIA (*Furie et al. 2011; Goldstein et al. 2011; Lindsberg et al. 2011*). Other known modifiable risk factors are (*Goldstein et al. 2006*): **obesity, physical inactivity, alcohol and drug abuse** (*Hillbom and Kaste 1978; Hillbom and Kaste 1983; Hillbom et al. 1995; Hillbom et al. 1999; Numminen et al. 2000b; Mostofsky et al. 2010; O'Donnell et al. 2010*), **hyperhomocysteinemia, infections and inflammation** including upper respiratory tract infections, caries, and parodontosis (*Syrjanen et al. 1988; Syrjanen et al. 1989*), **elevated CRP** (*Kaptoge et al. 2010*), **migraine** (*Schurks et al. 2009*), **sleep apnea and snoring** (*Palomäki et al. 1989*), but the effect of treating any of these is yet unknown (*Goldstein et al. 2006*). Even a diet rich in sausages has been identified as a stroke risk factor (*Larsson et al. 2011*). In addition to prevention of stroke, medications may also produce less severe strokes, as has been demonstrated with statins (*Elkind et al. 2005*) and beta blockers (*Laowattana and Oppenheimer 2007*).

Risk factors of stroke have steadily declined in Finland since the 1970's, where the best observational data comes from the eastern Finland provinces of North Karelian and Northern Savo, but has mainly been studied in populations younger than 75 years of age. Mean total serum cholesterol has declined from 6.9 mmol/l in 1972 to 5.3 mmol/l in 2007. Mean blood pressure has fallen accordingly, from 151/92 mmHg to 134/80 mmHg. Smoking has fallen from 50% to 30 % in men, but increased from 10% to 20% in women.

Obesity (body mass index above 30) is the only risk factor which has not declined, but rather increased from 11 to 25 % in men, and stayed stable at 22% in women (*Vartiainen et al. 2010*).

Risk Factors of Stroke

Summary points

1. Advanced age, male sex, non-white race, and a family history of stroke are the main non-modifiable risk factors of stroke, age being the most important.
2. Hypertension, dyslipidemia, smoking, excessive alcohol consumption, physical inactivity, and obesity are the main modifiable stroke risk factors.
3. Several other factors which are known to increase the risk of stroke exist, but the effectiveness of treating these is unknown.
4. The risk factors for ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage are similar, but they differ in their magnitude.
5. In Finland, hypertension, dyslipidemia, and smoking have declined steadily for 35 years, but there has been an increase in obesity.

2.4 Treatment of Stroke

Treatment of stroke includes multiple overlapping processes, all of which aim to preserve and restore the functions of the affected brain tissue. Acute interventions target tissue at risk; organized care delivers an optimal environment to prevent further damage to the brain and other organ systems; restorative rehabilitation enhances the plastic capabilities of the brain; and secondary prevention aims to avert stroke recurrence. All of these are started right after the stroke. Guidelines on the treatment of stroke have been published in the USA (*Adams et al. 2007; Bederson et al. 2009; Morgenstern et al. 2010; Brott et al. 2011; Furie et al. 2011*), Europe (*EUSI 2000; Olsen et al. 2003; Brainin et al. 2004; Steiner et al. 2006; ESO 2008*), and also in Finland (*Kaste et al. 1979; Simonen et al. 1989; Kaste et al. 2006; Lindsberg et al. 2011*).

2.4.1 Acute interventions

In all subtypes of stroke, brain damage due to ischemia or hemorrhage may progress over the first hours to days. Therefore, rapid recanalization of the occluded vessel in ischemic stroke can reduce final brain damage, and evacuation of hematomas and closure of ruptured vessels in hemorrhagic stroke can save viable tissue. All such attempts have risks involved, and may benefit some patients, while being harmful to others.

Thrombolytic therapy for stroke was first tested in the year 1958 with plasmin (*Sussmann and Fitch 1958*), and a full dozen different agents affecting the various steps of the coagulation and fibrinolytic cascades have been tested in humans since (*Meretoja and Tatlisumak 2006*). The only evidence-based recanalization strategy in ischemic stroke to date is recombinant tissue-type plasminogen activator alteplase, when used within 4.5 hours from symptom onset (*The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995; Hacke et al. 2008; Wardlaw et al. 2009; Lees et al. 2010*), with a number-needed-to-treat (NNT) of 5 to reach an excellent outcome if treatment is initiated within 1½ hours, 9 when administered from 1½ to 3 hours, and 15 if the delay is from 3 to 4½ hours (*Lees et al. 2010*).

While tenecteplase and desmoteplase were the latest rivals aiming at reducing the hemorrhagic complications and extending the time-window of thrombolytic therapy for stroke (*Meretoja and Tatlisumak 2008*), the latest trials of both substances failed (*Hacke et al. 2009; Haley et al. 2010*). A further study of desmoteplase is recruiting patients, but the current challenge is to deliver the effective alteplase treatment to all eligible patients, as the thrombolysis rates among ischemic stroke patients reported in Sweden (6.6% of the 18-80 year old patients in the year 2008) (*Eriksson et al. 2010*) and USA (5% of all age groups in the year 2009) (*Fonarow et al. 2010*) are low. It has been estimated that under ideal conditions thrombolytic rates could be around 25% (*CASPR Investigators 2005*). There are major differences between the USA and European labeling of alteplase for

stroke, and the more restricted labeling in Europe is likely to reduce thrombolysis rates, although many of the contraindications are not evidence-based (*Meretoja et al. 2010b*).

As only half of the occluded vessels re-canalize with intravenous thrombolysis (*Rha and Saver 2007*), more effective strategies have been sought. Enhancement of the thrombolytic agent with transcranial ultrasound has been shown feasible (*Alexandrov et al. 2004*). Intra-arterial thrombolysis with pro-urokinase has been shown effective, with a NNT of 7, but the drug is not licensed or available (*Furlan et al. 1999; O'Rourke et al. 2010*). Intravenous followed by intra-arterial approaches have been studied in small pilot studies (*Lewandowski et al. 1999; The IMS Study Investigators 2004; The IMS II Trial Investigators 2007*), and a larger IMS III trial is underway. Mechanical and ultrasound-based devices have been licensed for intra-arterial retrieval, stenting, or disruption of the blood clot, but none of these have been tested in randomized controlled trials (*O'Rourke et al. 2010; Molina 2011*).

When recanalization fails, or a very large infarction develops despite recanalization, there is a risk of malignant and fatal brain edema. Early decompressive surgery, i.e. hemicraniectomy, is life-saving in this context, and improves patient functional outcome, but has been tested in randomized controlled trials only in patients younger than 60 years of age (*Vahedi et al. 2007; Molina and Selim 2011*). Hypothermia is being tested in trials, but no effect has been shown so far (*Hemmen et al. 2010*).

For ICH, acute treatment can be conservative or operative. Activated recombinant factor VII has been studied in randomized double-blind placebo-controlled trials, but the promising results of the earlier trials (*Mayer et al. 2005*) could not be proven in the pivotal trial (*Mayer et al. 2008*). When coagulation disorders, thrombocytopenia, or medical anticoagulation are involved, fresh frozen plasma, vitamin K, and/or coagulation concentrates can be administered to stop the hemorrhage (*Morgenstern et al. 2010*). When the intracranial pressure (ICP) is elevated, reasonable treatment options include ventricular drainage, and surgical ICH removal. Trials on surgery are scarce (*Juvela et al. 1989; Mendelow et al. 2005*), and the recent guidelines state that for most patients, the benefit of surgery is unclear. Exceptions are patients with cerebellar hemorrhage with deteriorating consciousness and/or CSF blockage; these patients should be operated as soon as possible. Also some patients with large lobar hemorrhages close to the brain surface may benefit from surgery (*Morgenstern et al. 2010*). Most patients with ICH should be treated conservatively.

For aneurysmal SAH, the acute treatment options are open surgery clipping and intra vascular coiling of the aneurysm. The decision between these two treatment options can be made at individual patient level, and both options should be available in centers treating SAH patients. The procedure should be performed as early as possible (*Bederson et al. 2009*).

2.4.2 Organized inpatient care

Organized inpatient care of stroke patients has had various definitions, but usually refers to specialized hospital care of stroke patients involving a multidisciplinary team (nurses, doctors, therapists), in a distinct geographic area (stroke unit) (*Stroke Unit Trialists' Collaboration 1997; Stroke Unit Trialists' Collaboration 2007*). Different studies have been more or less strict as to whether other patients can be treated in a stroke unit, and the units studied have thus been either only for stroke patients, or included a mixed variety of other patients.

Over an average follow-up of one year, stroke ward care reduces the relative risk of death by 18%, NNT 22; death or institutional care by 14%, NNT 17; and death or dependency by 7%, NNT 24 (*Stroke Unit Trialists' Collaboration 2007*). Mobile stroke teams without a specific ward or unit are inferior in both patient outcome and cost (*Norrving and Adams 2006; Stroke Unit Trialists' Collaboration 2007*).

Stroke unit care can be delivered in various settings, either involving only acute patients for a few days (acute stroke unit), only rehabilitation patients after a delay of usually a week (rehabilitation stroke unit either solely for stroke patients, or mixed with other rehabilitation patients), or both (comprehensive stroke unit). Acute stroke care can be intensive, with constant monitoring, high levels of nursing, and possibility for life-support; semi-intensive, as above, but without life-support; or non-intensive (*Stroke Unit Trialists' Collaboration 2007*). The Cochrane review, gathering all available evidence, could find no difference in patient outcome between these various stroke unit types.

In a Finnish randomized trial over the years 1987 to 1989, before there were stroke units in Finland, patients treated at the department of neurology have been shown to have a better functional outcome than patients treated at the department of medicine. Patients treated by a multidisciplinary team at the department of neurology were able to leave the hospital on average 16 days earlier. Out of 100 patients, 13 more could be discharged home, and at 1-year follow-up 17 more were independent in their activities of daily life (*Kaste et al. 1995*). The comprehensive, intensive or semi-intensive, model of stroke unit care has since become dominant in Scandinavian and German stroke care. Swedish registries of observational data have repeatedly supported the use of stroke units (*Stegmayr et al. 1999; Glader et al. 2001; Terént et al. 2009*). Observational data from Germany also support a semi-intensive stroke unit over conventional care (*Walter et al. 2009*).

Efforts have been made to identify which components in stroke unit care count (*Langhorne and Pollock 2002*) and first detailed guidelines were published in Europe by the European Stroke Initiative (EUSI) in 2004 (*Brainin et al. 2004*) and have been updated by the European Stroke Organization (ESO 2008).

Organization of stroke care has advanced beyond stroke units and in-hospital phase, and it has been realized that a full chain of recovery should be involved, including primary prevention, emergency medical systems, acute care and rehabilitation, long-term follow-up, public education, community campaigns, and research (*NINDS Task Force 2003*). The concept of stroke centers has been developed to encompass these functions.

The Brain Attack Coalition in the USA published in the year 2000 consensus criteria for Primary Stroke Centers (PSC) (*Alberts et al. 2000*), later followed by criteria for even more specialized Comprehensive Stroke Centers (CSC) (*Alberts et al. 2005*), which more readily fulfilled the center-of-excellence concept including the whole chain of recovery. While stroke center designation has been shown to improve rates of thrombolytic therapy, no effect on patient outcome has been demonstrated (*Morgenstern et al. 2002; Lattimore et al. 2003; Rymer et al. 2003; Wojner-Alexandrov et al. 2005*). Despite this, the Joint Commission in the USA has certified stroke centers since 2003, and certification status may determine hospital reimbursements.

EUSI performed a survey in Europe to evaluate expert opinion on what should be included in primary and comprehensive stroke centers (*Leys et al. 2007b*). In a study of European stroke facilities in 25 European countries, only 8.5% of 885 hospitals involved in the treatment of stroke patients met the criteria for stroke centers (*Leys et al. 2007a*). Only 13.5% of stroke patients, i.e. one out of seven were admitted to these specialized centers. Thus, in Europe, a solid network of stroke centers is far from achieved. The ESO Taskforce for stroke unit certification is working to increase the number of certified stroke units and to improve the chance of future stroke patients to have access to high quality stroke care.

2.4.3 Rehabilitation

Less than one third of stroke patients fully recover; rehabilitation is an option for the rest (*ESO 2008*). Organized multidisciplinary rehabilitation of stroke patients is evidence-based medicine (*Langhorne and Duncan 2001*).

Numerous specific interventions have been evaluated:

- While physiotherapy in general is beneficial, especially if initiated early (*Van Peppen et al. 2004; Pollock et al. 2007*), movement constraint therapy (*Sirtori et al. 2009*), treadmill training (*Moseley et al. 2005*), or simultaneous bilateral training (*Coupar et al. 2010*) is not. Repetitive tasks improve ADL functions, but no benefit has been shown after the therapy is stopped (*French et al. 2007*). Over ground physical therapy gait training, and fitness training both improve patient speed, but no effect on disability has been shown (*Saunders et al. 2009; States et al. 2009*). Music therapy may be beneficial for training to walk after stroke (*Bradt et al. 2010*).

- Speech therapy for aphasia following stroke is effective in general (*Kelly et al. 2010*), but no specific techniques have been shown superior to one another. More intensive therapy is more effective. Speech therapy is as effective when administered by a trained volunteer or relative, as when administered by a therapist (*Kelly et al. 2010*). Therapies for dysarthria have not been studied (*Sellars et al. 2005*).
- Occupational therapy improves patient outcome and likelihood of independence in ADL functions (*Legg et al. 2006*), but not cognitive abilities (*Hoffmann et al. 2010*).
- Cognitive therapy does improve alertness and attention, but not memory, neglect, or independence (*Lincoln et al. 2000; Bowen and Lincoln 2007; Nair and Lincoln 2007*).
- No effective rehabilitation interventions for motor or speech apraxia (*West et al. 2005; West et al. 2008*), or sensory impairments (*Doyle et al. 2010*) have been identified.

In addition to stroke unit and other inpatient rehabilitation (*Langhorne and Duncan 2001*), also outpatient therapy is effective (*Outpatient Service Trialists 2003*). There is no evidence to support continuing rehabilitation for more than a year after stroke (*Aziz et al. 2008*), although effects of therapy administered six months after stroke are still noticeable, albeit they no longer affect ADL function (*Ferrarello et al. 2011*). Ultra-early rehabilitation, within 24 hours of stroke, is feasible, but adverse events and benefit are unclear (*Bernhardt et al. 2009*). Also people in permanent long-term care benefit from rehabilitation (*Forster et al. 2009*). Rehabilitation for stroke in Finland is far from optimal, large geographic variations exist on service availability, and there is much room for improvement (*Wikström et al. 2009*).

2.4.4 Secondary prevention

A quarter of stroke cases are recurrences (*Furie et al. 2011*), and all patients with a history of stroke must be considered at an increased risk for recurrent strokes. Secondary prevention should always be individually tailored, and depends on stroke subtype and etiology, as well as patient's risk factor profile, motivation, and cognition. Most ischemic stroke patients benefit from antithrombotic, antihypertensive, and lipid lowering medications, and some from carotid interventions. ICH patients mainly benefit from antihypertensives, while the secondary prevention of SAH is based on closure of aneurysms, possible screening for development of further aneurysms, and quitting of tobacco smoking. Life-style modifications are important in all stroke subtypes.

Antithrombotics

The efficacy of warfarin in the secondary prevention of stroke in atrial fibrillation patients has been shown in three trials, namely VA-SPAF (*Ezekowitz et al. 1992*), EAFT

(*European Atrial Fibrillation Trial Study Group 1993*), and SIFA (*Morocutti et al. 1997*). Combined, these trials showed a 51% annual stroke risk reduction when compared to antiplatelets (*Saxena and Koudstaal 2004*). Stroke secondary prevention with warfarin is evidence-based only in atrial fibrillation. For atherothrombotic stroke, antiplatelet drugs are more effective.

Acetylic salicylic acid (ASA) is 13% more effective than placebo in the secondary prevention of stroke (*Sandercock et al. 2008*). The combination of extended release dipyridamole and ASA is superior to ASA alone, as shown in ESPS 2 (*Diener et al. 1996*) and ESPRIT studies (*Halkes et al. 2006*). Clopidogrel showed a non-significant trend towards better secondary prevention than ASA in the CAPRIE trial (*CAPRIE Steering Committee 1996*) and was as effective as the combination of ASA and dipyridamole in the PROFESS trial (*Sacco et al. 2008*).

Antihypertensives

Antihypertensive medication is indicated after IS, even in normotensive patients (*Furie et al. 2011*). While many large studies, like ALLHAT (*ALLHAT Authors/Officers and Coordinators 2002*), LIFE (*Dahlof et al. 2002*), MOSES (*Schrader et al. 2005*), and ONTARGET (*Yusuf et al. 2008b*), have studied antihypertensives in secondary prevention of stroke, these did not include a placebo arm. The HOPE trial showed a 32% annual reduction in strokes with ramipril when compared to placebo, but this was not a stroke secondary prevention trial, as only 11% of the participants had a history of stroke (*Yusuf et al. 2000; Bosch et al. 2002*).

The proof of antihypertensive efficacy in stroke secondary prevention comes from the following trials and meta-analyses:

- PATS, indapamide vs. placebo, n=5665, relative risk reduction (RRR) 29% with active treatment (*PATS Collaborating Group 1995*)
- INDANA-meta-analysis of 8 smaller trials, mainly diuretics vs placebo, n=1087, RRR 29% (*Gueyffier et al. 1997*)
- PROGRESS, perindopril ± indapamide vs. placebo, n=6105, RRR 28%, the benefit coming mostly from the combination therapy, which benefited also normotensive patients (*PROGRESS Collaborative Group 2001*)
- ACCESS, candesartan vs. placebo, n=339, RRR 34% (*Schrader et al. 2003*)
- PROFESS, telmisartan vs. placebo, n=20 332, non-significant RRR 5% (*Yusuf et al. 2008a*)

Combined, these show a relative 16% annual decrease (OR 0.84; 95% CI 0.78 - 0.90) in stroke recurrence with antihypertensive medication use (*Meretoja 2009*). Diuretics, either alone or with ACE-inhibitors are the preferred initial choice for antihypertensive medications after stroke (*Furie et al. 2011*).

Lipid lowering

Lipid lowering strategies after IS have been given lower target values year after year. The most recent American guidelines suggest LDL cholesterol should be reduced by 50% after IS, or reduced to <1.8 mmol/l (*Furie et al. 2011*).

The proof of statin efficacy in stroke secondary prevention comes from two large trials. The HPS trial randomized 20 536 high-risk patients to simvastatin or placebo, and showed an annual stroke RRR of 25% (*Heart Protection Study Collaborative Group 2002*). However, most of the patients involved in this study were not stroke patients. In a post-hoc analysis of stroke, TIA, or carotid surgery patients (n=3280), no benefit from statin could be shown in secondary prevention of stroke, although the treatment reduced the combined end-point of vascular death, myocardial infarction, and stroke (*Collins et al. 2004*).

The only current proof of benefit from statin use after stroke comes from the SPARCL study, where 4731 patients were randomized to atorvastatin or placebo, and annual stroke recurrence decreased by 15% with active treatment (*Amarenco et al. 2006*).

Although both lower cholesterol (*Tirschwell et al. 2004; Lewington et al. 2007*), and statin use (*Heart Protection Study Collaborative Group 2002; Collins et al. 2004; Amarenco et al. 2006*) are associated with an increased risk of ICH, post-ICH statin use does not seem to result in increased ICH recurrence (*FitzMaurice et al. 2008*). Statins should be continued after ischemic stroke, as quitting is especially harmful (*Colivicchi et al. 2007*).

Carotid procedures

Tight carotid artery stenosis is a major risk factor for stroke, and it should be screened for acutely in ischemic stroke and TIA patients. Symptomatic stenosis patients benefit more from carotid endarterectomy (CEA), with NNT to prevent one annual ipsilateral stroke in cases of tight stenosis between 12 and 27 depending on how severe the carotid stenosis is (*Brott et al. 2011*), and lower when operated early within 2 weeks of symptoms (*Rothwell et al. 2004*). Asymptomatic stenosis operation NNT values are high, from 84 to 1351, and should be performed only in cases where perioperative risks are low (*Brott et al. 2011*). Carotid stenting is a therapy alternative to CEA, but has worse long-standing protective effect than CEA, does not reduce complications, and should be performed in selected patients only (*Rothwell 2010; Economopoulos et al. 2011*).

Lifestyle modification

Smoking should be quit, especially after a stroke. Counseling, nicotine products, and oral smoking cessation medications are evidence-based in helping quit smoking (*Furie et al. 2011*). Heavy drinking should also be quit because it is associated with increased risk of both ischemic and hemorrhagic stroke and quitting should be encouraged. It may be safe to drink 1 to 2 drinks per day, which may even reduce the risk of ischemic stroke (*Palomaki and Kaste 1993*), although not something to advise (*Furie et al. 2011*). Obesity and low physical activity are risk factors for stroke. Reduction in obesity and increase of

physical activity are likely to reduce other risk factors of stroke, such as hypertension, impaired glucose tolerance, and lipid disorders, and should therefore be encouraged. However, no studies have shown that smoking cessation, reduction of alcohol consumption, reduction of weight, or increase of physical activity would reduce stroke recurrence (*Furie et al. 2011*).

Treatment of Stroke

Summary points

1. Treatment of stroke is well guided by detailed national and international guidelines.
2. Recanalization should be attempted in ischemic stroke patients when possible. Only intravenous alteplase within 4.5 hours of symptom onset is evidence-based for this purpose.
3. Ruptured aneurysms should be closed in SAH patients, and choice between clipping and coiling is done on individual basis.
4. Most ICH patients do not benefit from ICH evacuation.
5. Acute stroke treatment should take place in a stroke unit.
6. Stroke centers, encompassing all the functions of the chain of recovery before and after a stroke unit, have been described, but their efficacy is unproven.
7. Rehabilitation after stroke is needed in most patients, is evidence-based as a whole, but data from randomized controlled trials on details and techniques is limited.
8. Secondary prevention of stroke should include antithrombotics, antihypertensives, and lipid lowering agents in most and carotid procedures in selected ischemic stroke patients, antihypertensives in ICH patients, and aneurysm closure in SAH patients.
9. All stroke patients should be given advice on life-style modification.

2.5 Outcome of Stroke

2.5.1 Mortality

Stroke caused 5.7 million deaths worldwide in the year 2004, 9.7% of all deaths (58.8 million), and second only to all cancers together (7.4 million, 12.6%) and ischemic heart disease (7.2 million; 12.2%) (*WHO 2008*). National income is a stronger predictor of stroke mortality than are cardiovascular risk factors. Age-adjusted mortality rates vary by a factor of 10 among countries (*Johnston et al. 2009*). Stroke causes 1/18 (5.6%) of all deaths in the USA. A 15% fall in absolute number of deaths, and a 45% decrease in age-adjusted death rate has been observed from 1997 to 2007 (*Roger et al. 2010*).

Figure 1 presents the official Finnish mortality statistics from 1969 to 2009. Statistics Finland reports that the data is otherwise comparable in time, but over the years 2005 - 2006 the classification was changed in such a way that pneumonia alone was no longer considered the cause of death if another long-term disease was mentioned in the death certificate. This decreased pneumonia deaths by about a third, and these cases were mostly coded as dementia or cerebrovascular disease (www.stat.fi, accessed 18th Jan 2011). It is noteworthy from the data in Figure 1, that although the total population has grown by 15%, from 4 614 277 to 5 351 427, and the number of population older than 75 years of age has more than tripled, from 120 962 to 427 079, the number of stroke deaths has decreased by 32%, from 6455 to 4380.

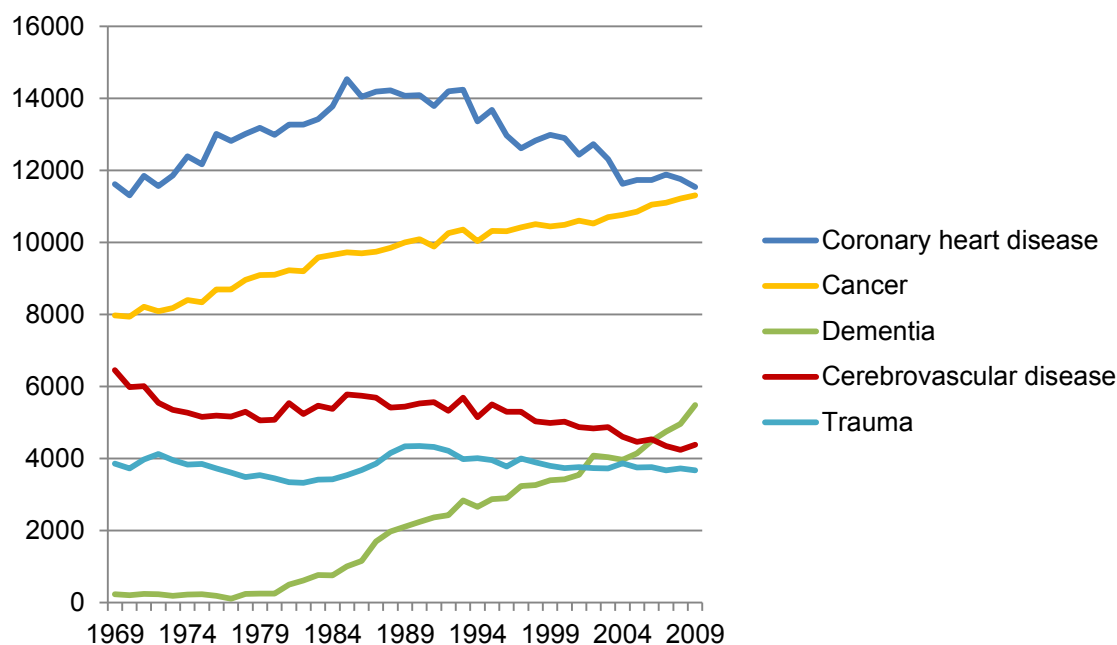


Figure 1. Trends in causes of death in Finland over the years 1969 to 2009.

The five most significant causes of death in the year 2009 are presented, which together comprised 73% of all deaths in that year (36 390 / 49 904).

Finnish age-adjusted mortality from cerebrovascular disease almost halved in the period of 1969 to 1982 (*Tuomilehto et al. 1986*). Most of the reduction was due to reduction in ICH (*Tuomilehto et al. 1984*). Over the years 1982 to 2009, the age-adjusted mortality has continued to decrease by another 56% (www.stat.fi, accessed 18th Jan 2011).

The decrease in stroke mortality could be either due to decreased incidence of stroke, or decreased case-fatality after stroke, but is most likely a combination of these (*Kotila 1984; Tuomilehto et al. 1993; Numminen et al. 2000a; Lehtonen et al. 2004; Sivenius et al. 2004*). Changes in classification of causes of death could be a third explanation, but this has been considered unlikely (*Sarti 1993; Sarti et al. 1993*).

2.5.2 Case-Fatality

Early case-fatality has been reported in most population-based incidence studies of stroke. In high-income countries, overall stroke one-month case-fatality has declined from around 35% in the 1970's to around 20% in the 2000's. It has been suggested that the reductions in early case-fatality rates reflect improved risk factor control and more widespread use of medications (ASA, antihypertensives, and statins) before stroke, rather than changes in acute care. Even in the 2000's, there was little difference in the early case-fatality rates between high-income and low to middle income countries among ischemic stroke (14% vs. 17%) or ICH patients (41% vs. 39%), but a larger difference in SAH patients (30% vs. 44%) (*Feigin et al. 2009*).

The 28-day case-fatality from all stroke has been 32% in North Karelia, and 38% in Espoo-Kauniainen in the 1970's (*Puska et al. 1974*), and the median survival after ICH in the 1972-3 was as low as 3 days (*Aho 1975*). The case-fatality rates depend strongly on stroke severity, patient age, and stroke subtype. Age-adjusted stroke severity has decreased in Finland from the 1972 to the 1991, as shown in two population-based registries (*Numminen et al. 2000a*).

According to the FINMONICA and FINSTROKE studies, 28-day case-fatality of all stroke has declined in the <75 year olds from 1983 to 1997 from 21.9% to 18.6% (*Sivenius et al. 2004*), and was 36.6% in the >75 year olds in the year 1997 (*Lehtonen et al. 2004*). The 28-day case-fatality rate for all stroke patients was thus 28.2% in the year 1997.

The likelihood of dying is permanently increased also in stroke patients surviving the acute phase. All-cause annual fatality rates of stroke survivors after one year since stroke are about twice that of the age and sex matched general population (*Hankey et al. 2000*).

2.5.3 Prevalence

Prevalence is more difficult to measure than incidence or mortality, and estimates are either based on extrapolations from incidence and mortality data, or from surveys. The worldwide prevalence of stroke has been estimated at 30.7 million in the year 2004, and 12.6 million are living with moderate to severe disability. A total of 9.6 million stroke survivors live in Europe (*WHO 2008*). The prevalence of stroke in the USA has been estimated as 7 million stroke patients, 3% of the population aged 20 or over (*Roger et al. 2010*). This figure is expected to increase to 4% by the year 2030 (*Heidenreich 2011*).

In Finland, the prevalence of stroke was estimated in the SII Mobile Clinic Health Examination Survey in 1973 to 1976, based on the question: "Have you had a stroke that has been diagnosed by a doctor?". Of the patients who answered affirmatively, only 53% truly had had a stroke after review of medical data. A national stroke prevalence of 26 300 (0.6%) for the whole country was estimated (*Aho et al. 1986*).

In a prevalence study performed in the Jyväskylä area in 1989, 471 stroke patients in institutional care were identified, which represented about half of all stroke survivors. The data on total prevalence presented in the study is somewhat ambiguous, but has been estimated at 41 000 (0.8%) in the whole of Finland (*Rissanen 1992; Kaste et al. 2006*).

The Health 2000 survey in the year 2000 was carried out in a population of 6770 adults aged over 30 years of age. Stroke prevalence, based on an interview and a physical examination, was 2.3% in men and 1.3% in women (*Aromaa and Koskinen 2004*). This corresponds to about 60 000 people in the population aged over 30 years of age, or 1.2% of the total population in the year 2000.

2.5.4 Disability, late post-stroke complications, and quality of life

Disability and functional outcome

Worldwide, stroke is the sixth most important cause of disability, as measured by disability adjusted life years (DALY), after lower respiratory tract infections, diarrhea, depression, ischemic heart disease, and HIV/AIDS. Stroke is responsible for a loss of 46.6 million DALYs annually, 3.1% of all DALYs lost due to disease. In high-income countries, stroke is the number three cause of disability, after depression and ischemic heart disease, and accounts for 4% of all disease-related disability (*WHO 2008*).

Validated scores to evaluate functional outcome after stroke have been developed (*Kasner 2006*), such as the modified Rankin Scale (mRS) (*Rankin 1957; van Swieten et al. 1988; Banks and Marotta 2007*), and Barthel Index (*Mahoney and Barthel 1965*). In stroke trials, it has become practice to measure outcome at 3 months after stroke, and the mRS in its simplicity is the most widely used measure. The mRS does not have a ceiling effect like the Barthel Index.

Functional outcome has been looked at also in Finnish population-based studies. Aho evaluated the patients for 3-month mRS, and 14% of patients had an excellent outcome (0-1), 39% a good outcome (0-2), 46% a moderate outcome (0-3), while 40% were dead (6) (*Aho 1975*). In the study by Rissanen, mRS was evaluated at one year, when 15% (40/266) had an excellent outcome, 33% a good outcome, 49% a moderate outcome, and 37% were dead (*Rissanen 1992*).

Late post-stroke complications

In addition to the obvious motor, speech, sensory, and visual deficits caused by a stroke, several complications may develop later on as a result of the stroke.

Low mood is a natural reaction to disability caused by a stroke, but can become **depression** if prolonged and severe. Post-stroke depression is common, but the estimates in studies vary from 18% to 61% depending on criteria and time of evaluation (*Gainotti and Marra 2002*). Although early depression predicts poor outcome (*Pohjasvaara et al. 2001; Willey et al. 2010*) the mood disorder is likely to resolve spontaneously as time goes by (*Hackett et al. 2005b*), which may be augmented with support systems (*Kotila et al. 1998*) and medications (*Hackett et al. 2005a*). Antidepressants may improve rehabilitation results (*Chollet et al. 2011*). Depression in caregivers of stroke survivors is common (*Berg 2010*).

Dementia is a frequent outcome after stroke, either due to the stroke, due to other pathology existing in the elderly patients, or a combination of these (*Leys et al. 2005; Erkinjuntti 2007*), and can range from mild cognitive decline to severe dementia, together called vascular cognitive decline (*Erkinjuntti and Gauthier 2009*). Post-stroke or vascular dementia can be defined with various criteria which can give widely differing estimates of prevalence in the same patient population, from ~6% to ~27% (*Wetterling et al. 1996; Pohjasvaara et al. 1997*). Also dementia prior to stroke is common, and strongly affects the outcome of stroke patients (*Henon et al. 2003; Melkas et al. 2009*). Unfortunately there are no evidence-based specific medications for vascular dementia (*Kavirajan and Schneider 2007*), and the treatment concentrates on stroke secondary prevention and control of symptoms.

Epilepsy in the old age is most often a result of a prior stroke, stroke is the most common cause of secondary epilepsy in all age groups, and 2-4 % of stroke patients develop epilepsy (*Bladin et al. 2000; Camilo and Goldstein 2004; Benbir et al. 2006*). Seizures at the acute phase of stroke rarely reoccur, but more than half of patients with later seizures do develop epilepsy, and these patients require antiepileptic medications (*De Reuck et al. 2008b*). Certain infarct localizations, cortical involvement, and temporo-parietal regions, and more severe strokes predict a higher risk of post-stroke epilepsy (*Bladin et al. 2000; De Reuck et al. 2008a*), while the risk in hemorrhagic and ischemic strokes are fairly similar (*Bladin et al. 2000*).

Spasticity is a common complication one year after stroke, affecting 17% to 39% of patients (*Watkins et al. 2002; Lundstrom et al. 2008*), and should be treated when it interferes with activities of daily living (*Brainin et al. 2011*). The treatment is usually multifactorial, and options include physiotherapy, systemic antispasmodic drugs, and botulinum toxin injections (*Brainin et al. 2011*).

Other common late complication of stroke include **pain** (*Jonsson et al. 2006*), **apathy** (*Brodaty et al. 2005*), **fatigue** (*Glader et al. 2002*), **anxiety** (*Morrison et al. 2005*), and chronic posttraumatic **stress symptoms** (*Bruggemann et al. 2006*).

Quality of life

The perceived quality of life (QOL) after severe stroke may be judged very low, even negative i.e. worse than death, by healthy subjects, but much higher in stroke victims themselves (*Murphy et al. 2001*), reflecting the adaptive capabilities of the human psyche. In severe stroke, this coping usually takes at least half a year (*Darlington et al. 2007*). Measuring QOL in stroke patients with communication problems is a special challenge, but proxy ratings i.e. rating of QOL by a close relative or caregiver, have been deemed fairly valid when 6 months have passed since the stroke (*Pickard et al. 2004*). Reviews of QOL after stroke emphasize the main determinant of QOL, the initial stroke severity (*Post et al. 2001; Tengs et al. 2001; Carod-Artal and Egido 2009*). Stroke impact on caregiver QOL is significant when considering the total burden of the disease (*Carod-Artal et al. 2009*).

QOL has been measured in Finland, in 85 stroke survivors in Oulu (*Kauhanen et al. 2000*), and in the Health 2000 study in 6770 citizens, out of which about 200 were stroke survivors (*Aromaa and Koskinen 2004; Saarni et al. 2006*). In the latter study, stroke diagnosis was based on self-reporting (2.8% prevalence), about 1/3 of which is incorrect after a physician's assessment (*Aromaa and Koskinen 2004*). Among 29 chronic conditions evaluated, stroke was the fifth most important cause of loss of QOL, after Parkinson's disease, arthrosis, anxiety disorders, and depression. Different QOL instruments did not show uniform results (*Saarni et al. 2006*).

Outcome of Stroke

Summary points

1. Stroke is the number 3 cause of death worldwide, after cancer and coronary heart disease, accounting for 5.7 million deaths, or 10% of all deaths.
2. About one in five stroke patients dies in the acute phase of stroke, and death is more likely in the old, with severe strokes, in ICH or SAH patients, and in low income countries.
3. Stroke is a major cause of disability in the population. Late post-stroke complications, such as depression, cognitive decline, epilepsy, and spasticity contribute to this disability.
4. In Finland, age-adjusted stroke mortality has fallen annually by 2.5% in the 70's to 80's, and by 2% annually since, reflecting decrease in both incidence and case-fatality.
5. Finnish stroke prevalence is increasing with improved survival.
6. Functional outcome and QOL after stroke have been measured in too few Finnish high-quality epidemiological studies to make conclusions about recent trends.

2.6 Cost of Stroke

Cost of stroke patients has been estimated to constitute between 1.6% and 6.9% of total healthcare costs in developed countries, with the latest estimates at around 3% (*Evers et al. 2004*). The direct medical costs of stroke in the USA are estimated at US\$ 28.3 Billion in the year 2010, and this is expected to more than triple to US\$ 95.6 Billion by the year 2030 (2008 currency). During the same time, the indirect costs of stroke are estimated to increase from US\$ 25.6 Billion to 44.4. Billion (*Heidenreich 2011*).

Cost of illness studies on individual patients

Cost of illness studies can be performed either top-down, i.e breaking the total sum of healthcare costs to their components, or bottom-up, i.e. from individual patient data. A latest systematic review of stroke cost literature was performed in the year 2009 (*Luengo-Fernandez et al. 2009*) and identified 120 studies with patient-level data on at least 20 patients from OECD countries. There were 6 larger studies with more than 10 000 patients: (*Mitchell et al. 1996*), n = 37 000; (*Chan et al. 1997*), n = 76 400; (*Samsa et al. 1999*), n = 49 000; (*Reed et al. 2001*), n = 31 000; (*Deutsch et al. 2006*), n = 58 000; (*Caro et al. 2006*), n = 19 000, while most studies included a few hundred patients. All of the studies were from 15 countries, and half of them published from data of USA, UK, or Swedish patients. There was significant variation in the cost estimates in these studies. Almost half of the studies evaluated only initial hospitalization costs. In the remaining studies, only few analyzed which of the costs were attributable to stroke based on previous resource use (n=7). Of all 120 studies, only 8 reported IS, ICH, and SAH costs separately. Mean 1-year costs of stroke or ischemic stroke in year 2006 values was US\$ 28 500, but variation between studies was huge, ranging from US\$ 7300 to US\$ 146 000. Variation was mostly explained by differences in costs between countries, but variance within countries was also large (*Luengo-Fernandez et al. 2009*).

Lifetime costs

Lifetime direct costs per stroke patient have been estimated in some studies. In the USA, these have been estimated, in year 1990 US\$ with 5% discounting of future costs, to be 44 000 for IS, 33 000 for ICH, 61 000 for SAH, and 44 000 for total stroke (*Taylor et al. 1996*). In Sweden, after some earlier cost of stroke studies (*Terént 1983; Persson et al. 1990; Thorngren and Westling 1991; Asplund et al. 1993*), these have been calculated, in 1991 currency value and discounted at 5% per annum, to be US\$ 73 000, of which US\$30 000 was associated with stroke and the remaining 60% with old age and other disease (*Terént et al. 1994*). The lifetime cost of a stroke patient in the Netherlands, in 1991 currency and no discounting, has been estimated for total stroke US\$ 41 000, US\$ 43 000 in IS patients, and US\$ 26 000 in ICH patients (*Bergman et al. 1995*). An estimate from Australia, in the year 1997 currency and 5% per annum discounting, was US\$ 34 000 (*Dewey et al. 2001*), later also reported according to subtype to be US\$ 32 000 for IS and US\$ 56 000 for ICH (*Dewey et al. 2003*). These figures also included indirect costs, which were less than 4% of total costs. A more recent estimate from Germany, reported in 2004

currency value, was 50 500 €, or 43 100 € after 3% discounting (*Kolominsky-Rabas et al. 2006*).

Costs in Finland

Total healthcare spending in Finland corresponded to 8.4% of gross domestic product (GDP) in the year 2008, which is below OECD average 9.0%. The public sector finances 74% of these costs, close to OECD average of 73% but lower than in most European countries (*OECD 2010*). In Finland, the lifetime cost of stroke has been estimated in one previous study, based on data from Jyväskylä region in the 1980's (*Kaste et al. 1998*). In 1991 currency, discounting of 5% per annum, the estimate was US\$60 000, of which more than 90% was stroke-related. This corresponded to 6.1% of total healthcare costs, high in international comparison. The indirect costs may be, depending on estimate, either as large as the direct costs, or with the friction model, only 30% of the direct costs (*Fogelholm et al. 2001*).

Costs attributable to stroke

One-year costs of the year immediately prior to first-ever stroke have been reported in two Swedish studies as being in the amount of 53% (*Terént et al. 1994*) and 6% (*Zethraeus et al. 1999*) of the costs over the year immediately post stroke. The difference has been thought to be due to difference in age structure between the studies (*Ekman 2004*). In the USA, the costs one year prior to stroke have been in the amount of 30% of the costs of the first year of stroke (*Leibson et al. 1996*).

Cost-effectiveness of specific components of care

The costs associated with possible improvements in the primary prevention of stroke and myocardial infarction in the USA have been estimated, and the only intervention that was cost-saving was tobacco cessation campaigns. Low-cost antithrombotics had low cost per QALY, but the primary prevention interventions treating hypertension, diabetes, hypercholesterolemia, and obesity cost between 17 000 to 270 000 USD per QALY gained (*Kahn et al. 2008*). Primary prevention in the population may thus not automatically be a cost-effective way to fight stroke, although it has a huge potential to reduce stroke (*Cadilhac et al. 2007*), and from the human suffering point of view is preferred. Primary prevention with warfarin in atrial fibrillation is an exception, with good cost-effectiveness (*Gustafsson et al. 1992; Mercaldi et al. 2011*). Although stroke unit care is very effective, it is also expensive, and the data on cost-effectiveness of stroke unit care is controversial (*Meretoja et al. 2010a*). ASA, blood pressure medications, and statins have been considered cost-effective in ischemic stroke secondary prevention in general, while more expensive medications and interventions perhaps only in selected patients (*Hankey and Warlow 1999*).

Cost of Stroke

Summary points

1. Treatment of stroke patients is expensive and consumes about 3% of all healthcare resources in developed nations.
2. Cost of stroke has been studied in 15 OECD countries, mostly in the USA, UK and Sweden.
3. In some studies ICH patients have had higher lifetime costs, while in others IS patients have been more expensive. Most studies do not report these separately.
4. It is unclear how much of the costs of stroke patients actually are caused by the stroke, as old age and comorbidities contribute significantly to the costs of these patients.

3 AIMS OF THE STUDY

- I To set up a nationwide database for monitoring stroke in Finland, using data from existing national registries.
- II To describe trends in national stroke case-fatality, and identify possible treatment-related associations on these trends.
- III To test whether treatment in a stroke center is associated with patient outcome.
- IV To describe the direct healthcare costs of stroke in Finland.

4 PATIENTS AND METHODS

4.1 The PERFECT project, organization, and timetable

The PERFECT project was started in the year 2004 as a research co-operation between health districts, Social Insurance Institute (SII; KELA in Finnish), and the National Research and Development Centre for Welfare and Health (STAKES). The project has been co-ordinated by the Centre for Health and Social Economics (CHESS) of STAKES. STAKES has merged with the National Public Health Institute (KTL) from the beginning of the year 2009, to form the National Institute for Health and Welfare (THL).

The PERFECT project aims to develop methodologies for systematic use of register-based data in the assessment of effectiveness and costs of major diseases. Seven costly diseases are modeled: stroke, myocardial infarction, breast cancer, schizophrenia, very preterm infants, hip fracture, and total hip arthroplasty.

Research professor Unto Häkkinen is the director of CHESS and the whole PERFECT project. There was a general methodological group within CHESS to develop the methods involved in cost approximation and benchmarking. In addition to this, each of the disease groups had a steering group consisting of clinical experts and CHESS personnel. The PERFECT Stroke project included the following neurologists and CHESS experts:

Atte Meretoja (secretary)	Helsinki University Central Hospital
Markku Kaste	Helsinki University Central Hospital
Aimo Rissanen	Jyväskylä Central Hospital
Juhani Sivenius	Kuopio University Hospital
Matti Hillbom	Oulu University Hospital
Terttu Erilä	Tampere University Hospital
Reijo Marttila	Turku University Hospital
Risto O. Roine (chairman)	Helsinki University Central Hospital (-2006), Turku University Hospital (2006-)
Merja Juntunen	National Institute for Health and Welfare / CHESS
Miika Linna	National Institute for Health and Welfare / CHESS
Unto Häkkinen	National Institute for Health and Welfare / CHESS

In addition, systems analysts' Eija Teitto (April 2004 to May 2005), Antti Liski (June 2005 to November 2006), and Juha-Pekka Konttinen (December 2006 to April 2007) contributed to the early development of the PERFECT Stroke methodology, and chief nurse Anne Puumalainen of the Helsinki University Central Hospital Stroke Unit attended several planning meetings in the early years. The PERFECT Stroke steering group convened 4 times, in addition to which a small taskforce (Meretoja, Kaste, Roine, Häkkinen, Linna, and the current systems analyst) had 24 meetings over the years 2004 to 2008 to develop the presented methodology.

The study was initiated in the first planning meeting on 5th April 2004. The details of coding, episode formation, and measurable definitions were done over the next two years. After approval of the regulative authorities, the large national registries were linked to obtain the data. The first database was formed in the summer of 2007 and the first standard reports published in late 2007 (*Meretoja et al. 2007*). Some corrections and methodological changes were made to the episode definition and coding the next year, and annual reports have been produced since, currently for the patients of the years 2003 to 2008, available in Finnish at http://www.thl.fi/fi_FI/web/fi/tutkimus/hankkeet/perfect.

No ethics committee approval or patient consent was required according to Finnish law, as the patients were not contacted, and the data was anonymized so that individual patients were not identifiable to the researchers.

4.2 PERFECT Stroke dataset sources, patient selection, and register linkage

Each Finnish citizen and permanent resident has a unique personal identification number, a system started in the year 1964, with full nationwide coverage in the year 1968 (*Gissler and Haukka 2004*). This number is comprehensively used in all administrative registries to identify a person, allows for reliable follow-up of a person within a registry, and makes linkage of various registries possible.

The main source of the PERFECT project is the Finnish national Hospital Discharge Register (HILMO). This registry has been operating in Finland since 1967 and is run by THL (formerly STAKES). The HILMO register contains all hospital treatment episodes, including information on provider of care, first and last date of the episode, a primary diagnosis, several secondary diagnoses, and procedures performed during the hospital episode. In the year 1994, all social institutions, such as nursing homes, were added to HILMO (*Gissler and Haukka 2004*).

A stroke patient is identified from the HILMO with an ICD-10 primary diagnosis of a cerebrovascular disease (Table 1).

Table 1. *Stroke subtype classification in the PERFECT Stroke project.*

ICD-10 code	Stroke subtype	Abbreviation
G45	Transient ischemic attack	TIA
I60	Subarachnoid hemorrhage	SAH
I61	Intracerebral hemorrhage	ICH
I63	Ischemic stroke	IS
I62, I64-I68	Other cerebrovascular disease	OTH

Stroke syndromes (G46) were classified according to etiological subcode (I60 to I67), i.e. G46*I63.2 equals ischemic stroke.

Only first occurrences are included. If a patient has a previous ICD-10 code I60-I69, or a corresponding ICD-9 code of 430-434 or 436-438 in the HILMO registry, they are excluded. Previous TIA is not an exclusion criterion. Thus TIA-patients may appear in the database twice; if they are first hospitalized for a TIA and later for a stroke. Previous cerebrovascular disease diagnoses are checked for in HILMO from year 1987 onwards.

The patients identified with this approach are linked with personal identification numbers to the national CDR and the registries of SII. The CDR is only checked for to see if the patient has died, irrespective of cause. The registries of SII are used to check for any prescription medication purchases one year prior and one year post stroke, use of private medical services, and costs associated with both medications and private medical services. Also the SII Registers on Social Benefits are utilized to look for special reimbursement of medications in long-standing diagnoses. Sick leaves, and a linkage with the Registry of Pensions under the Finnish Center for Pensions, is also available, to estimate possible indirect costs due to lost productivity, but they are not reported, as indirect costs are outside the scope of this study. A distinct portion of HILMO, the discharge registry of social institutes, “social-HILMO”, is utilized in evaluating long-term institutional care, and direct costs associated with this care. For details of each of these registers, please see descriptive article (*Gissler and Haukka 2004*).

4.3 Forming an episode

An episode of care is formed from the data in HILMO. A patient has entries in the registry for each single hospital treatment according to treating specialty. For transfers between specialties, e.g. from internal medicine to neurology, separate entries are formed. For the purpose of the PERFECT Stroke database, these entries are joined, to estimate the total consecutive episode of in-patient care within and between hospitals. An episode starts with the first cerebrovascular disease diagnosis, and ends when the patient dies, is discharged and transferred home, or to a nursing home. New hospitalizations thereafter start a new episode.

Sometimes a patient has their stroke while already hospitalized for another reason, sometimes the primary diagnosis is uncertain at the first hospital, and sometimes there are several 1-day episodes for a single day, when a patient is rapidly transferred from one hospital to another. If the episode starts with multiple different concurrent or consecutive cerebrovascular disease diagnoses, one of these has to be chosen as the subtype according to which the episode is classified. As hemorrhagic stroke diagnoses are more likely to be made only with positive diagnostic findings, while ischemic stroke diagnoses or undefined stroke may be diagnosed with clinical suspicion only, the diagnoses are considered to be most likely in the following order: SAH, ICH, IS, Other cerebrovascular disease, TIA. These variations are depicted in Figure 2.

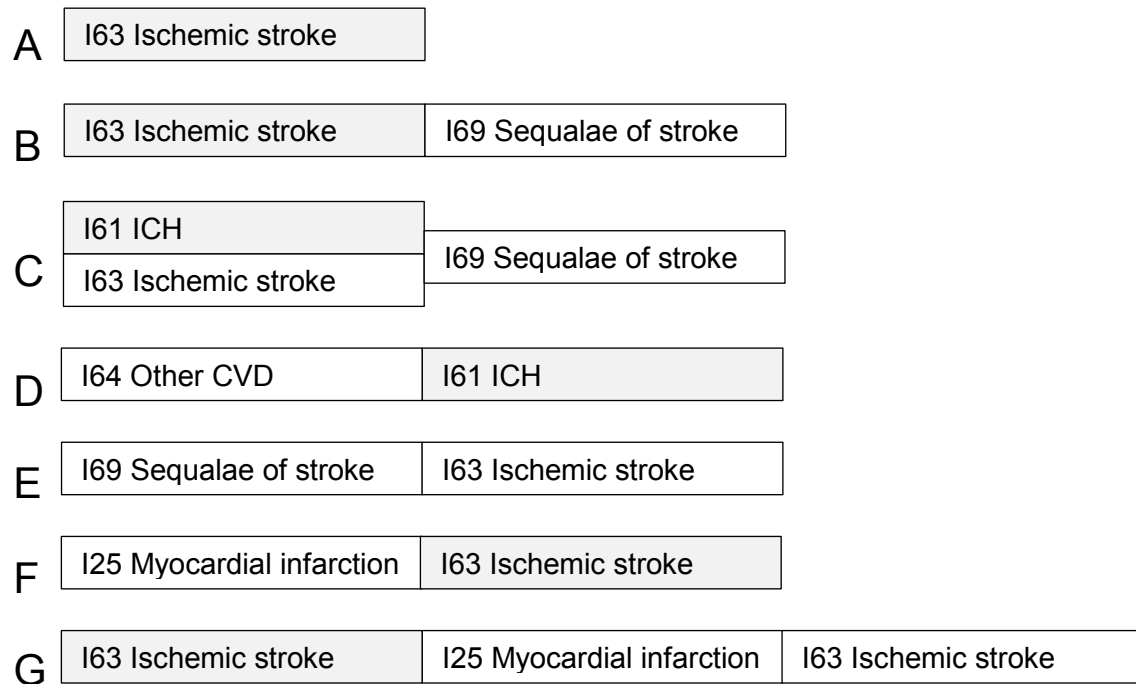


Figure 2. Different situations of forming an episode and classifying stroke subtype.

A. Only one discharge with cerebrovascular disease, classified as ischemic stroke (IS), with start and end dates of episode those of the record. B. An acute hospital stay, followed by a rehabilitation stay. Classified as IS, ending at end of continuous hospital stay (end of sequelae). C. Two records on the same day, with different diagnoses. Episode classified as ICH, as this diagnosis is considered to be more likely to be correct. D. First an unclassified stroke diagnosis, directly followed by an ICH diagnosis. The latter is considered correct, and the date of stroke is the start date of unclassified stroke record. E. The first record is sequelae of stroke. The patients is likely to have a history of stroke, even if a new one may have developed. Excluded from PERFECT. F. A non-stroke diagnosis, followed by a stroke diagnosis. Classified as IS. Date of stroke is the beginning of IS record, not beginning of hospital stay with myocardial infarction. G. IS episode, with another diagnosis in-between and later followed again by an IS diagnosis. Not considered a recurrence.

Lengths of stay (LOS) are counted for several aspects of the care:

- first hospital discharge entry = initial treating unit
- first episode, including acute care and rehabilitation, until discharged home or to a nursing home
- all other later hospital care within a year of stroke = re-hospitalizations
- total in-patient days within a year of stroke = b) + c)
- the LOS of care with a stroke primary diagnosis of all episodes included in d)

4.4 Definitions of procedures, medications, and comorbidities

Procedures are coded as part of the HILMO discharge record using the Nordic casemix center NCPS+ procedure codes (<http://www.nordcase.org/eng/ncsp/>), and some were included in the PERFECT database. Of interest in ischemic stroke were carotid endarterectomy (PAF*) and thrombolytic therapy (AAL10); in ICH, hematoma evacuation (AAD15 and AAB30); in SAH, aneurysm closure (AAC10 and AAL10); and in both SAH and ICH, procedures to control elevated CSF pressure (AAF*).

Data on medication use was retrieved from the registry of prescription medication purchases of SII. The registry was scanned one year prior and one year post stroke for each patient, and a single entry was considered to signify that the patient had been prescribed that medication and did purchase it. Antithrombotics, antihypertensives, and statins were of primary focus, but also diabetes medications, antidepressants, and dementia medications were of interest. Of the antithrombotic medications, ASA is prescription-free, and thus its use cannot be followed. Also antiepileptic medications would have been of interest, but are used for such a variety of indications that conclusion on their use would have been difficult. The medications being evaluated are listed in Table 2.

Table 2. *Medication purchases being evaluated in the PERFECT Stroke project, and corresponding Anatomical Therapeutic Chemical Classification System (ATC) codes.*

Medication	ATC-code
clopidogrel	B01AC04
dipyridamole	B01AC07 and B01AC30
varfarin	B01AA03
statins	C10AA*
ACE-inhibitors	C09A*-B*
AT II antagonists	C09C*-D*
betablockers	C07*
calciumblockers	C08*, C07FB*, C09BB*
diuretics	C03*, C07BB*, C09BA*, C09DA*
insulin	A10A*
oral diabetes medication	A10B*
dementia medication	N06D*
antidepressants	N06A*

Several comorbidities, considered clinically relevant and with potential to influence stroke subtype, severity, and patient outcome, were included in the PERFECT Stroke database. Information on comorbidities was collected from several overlapping sources:

1. Medication purchase data was evaluated one year prior to stroke, as explained above.
2. SII Special reimbursement codes for chronic disease were evaluated for codes active at the time of the stroke.
3. Previous hospital discharge register records were scanned for primary diagnoses from year 1987 onwards.

The codes used for finding the comorbidities are listed in Table 3. If any of these methods suggested comorbidity, the patient was considered to have that comorbidity.

Table 3. *Comorbidities being evaluated in the PERFECT Stroke project, and the corresponding coding.*

Co-morbidity	ICD-10	ICD-9	SRC	ATC-code
Hypertension	I10*-I15*	40*	205	C03*, C07*†, C08*, C09*
Coronary heart disease	I20*-I25*	410*-414*	206	-
Atrial fibrillation	I48*	4273*	207	-
Cardiac failure	I50*	428*	201	-
Peripheral artery disease	I70*	440*	-	-
Diabetes	E10*-E14*	250*	103	A10A*, A10B*
COPD and asthma	J44*-J46*	4912*, 496*, 493*	203	R03*
Alcoholism/drug abuse	F10*-F19*	291*, 304*, 305*	-	-
Dementia	F00*-F03*, G30*	290*, 3310*	307	N06D*
Depression	F32*-F34*	2960*, 2961*, 2069*	-	N06A*
Parkinson's disease	G20*	332*	110	N04B*
Other mental disorder	F20*-F31*	295*-298* except for 2960*, 2961*, 2069*	112, 188	N05A* except for N05AB04 & N05AB01
Cancer	C00*-C99*, D00*-D09*	140*-208*	115, 116, 117, 128, 130, 180, 184, 185, 189, 311, 312, 316	L01* except for L01BA01

ICD-10 = International classification of diseases Finnish version 10 (years 1996 onwards)

ICD-9 = International classification of diseases Finnish version 9 (years 1986-1995)

SRC = Social insurance institution (SII) special reimbursement code

ATC = Anatomical Therapeutic Chemical Classification System

* = any ending of the code

† = beta blocker alone not considered hypertension if patient has coronary heart disease or atrial fibrillation

4.5 Stroke center classification

Information on in-hospital processes is scarce in the hospital discharge register, and thus cannot be reliably evaluated on individual patient level, except for certain procedures mentioned earlier. To be able to evaluate the effect of differences in hospital resources and processes on patient outcome, an external data source had to be used.

The Finnish Stroke and Dysphasia Association had organized an audit of acute stroke care in Finland in the year 2003, described in detail elsewhere (*Roine et al. 2006*). A re-audit was performed in year 2006 (*Puumalainen et al. 2006*). Based on these two audits, all Finnish hospitals were classified, according to the Brain Attack Coalition (BAC) criteria (*Alberts et al. 2000; Alberts et al. 2005*), as Comprehensive Stroke Centers (CSC), Primary Stroke Centers (PSC), or General Hospitals (GH). All the criteria had to be met in order to fulfill the CSC or PSC classification, as described in detail in Table 1 of study III.

4.6 Estimation of costs

For the purpose of this study, only direct healthcare costs were evaluated. A societal perspective was used, which includes the healthcare costs irrespective of payer; usually the health district for acute care; either health district or commune for early rehabilitation; and sometimes the SII or other insurance company for long-term rehabilitation. Also co-payments by patients were included in the costs, which constitute on average 4% of public specialist care costs, 9% of general practice costs, 21% of nursing home costs, 31% of medication costs, and 75% of private medical services (*Pekurinen et al. 2010*). Altogether, co-payments by patients financed 19.4% of the Finnish healthcare in the year 2008 (*OECD 2010*). Although a societal perspective was used, only direct healthcare costs were included, which leaves indirect costs, such as lost productivity, outside the scope of this paper.

The methodology for estimating costs in the PERFECT project is generic for all the disease groups, not specific for stroke. The stroke project steering group was not involved in the development of the methodology in this respect, but this was rather done by a methodological group within CHESS. The methods presented are an extension and improvement of an earlier CHESS hospital Benchmarking methodology, which was fully hospital-based, and did not evaluate episodes of care.

The costs in the PERFECT project were evaluated with different methodology for in-patient care, outpatient visits, and medication purchases.

To evaluate the costs of **in-patient care**, a costing database, based on national weighted diagnosis related group (DRG) daily costs and patient-level data on DRG days, was used. The optimal approach would have been to use detailed patient-level in-hospital cost data, broken down to components, but most hospitals in Finland do not have such sophisticated

costing systems implemented, and in any case there would have been differences in costing methodology between hospitals, which would have made the data incomparable.

Therefore, a standard costing database was used, based on data from the Helsinki and Uusimaa Hospital District (HUS), which includes a population of 1.5 million inhabitants, 30% of the Finnish population. HUS has a detailed sophisticated costing system with individual patient-level cost data on laboratory tests, imaging, procedures, outpatient visits, and ward-days incorporating all ward personnel costs, medications, and overheads. Using the HUS data for all patients treated for any reason, each patient care record was classified according to the Nordic DRG system, version 2001, in DRG categories, and mean costs for each category per days spent in that category were calculated. Day-surgery was grouped separately within DRG groups.

In the next step, all the in-patient care for any reason in Finland in the year 2003, as retrieved from the HILMO database, was classified similarly to DRG groups. The relative costs per day of each HUS DRG category were then scaled to national data so that the relative cost weight of an average DRG category received a value of 1. Thus the relative costs between DRG groups were assumed to be equal in all parts of Finland. With these DRG costs, the national total costs of healthcare were annually distributed among the total number of national DRG days, to get annual cost per DRG day in each DRG group. To evaluate true costs per patient, these annual national DRG-specific daily costs were then applied to individual patient data: (Number of days spent in DRG A) x (National daily cost of DRG A for that year) + (Number of days spent in DRG B) x (National daily cost of DRG B for that year) etc. For long-term and psychiatric inpatient care, fixed national costs were used, taking nursing intensity into account. All costs were recalculated annually.

Costs of **outpatient visits** in public hospitals were valued with similar methodology as in-patient costs, again using HUS costing data, but now grouping visits not by DRG group, but by treating specialty and acuteness (emergency visit or scheduled visit). Again these visit costs were calculated annually, and used for the whole country. For private outpatient visits, costs were derived from the SII registers. For general practice (GP) visits, no national registry exists. Thus GP costs were not included in the PERFECT database, and neither were community outpatient nursing costs

Costs for **outpatient medications** were derived from the SII registry of prescription medications, and thus are true patient-level costs. This registry only includes medications which require a prescription. Over-the-counter medications are relatively in-expensive, so their effect on costs would have been small. The registry does not include medications administered by hospitals or GPs, such as drug infusions, as these are included in the costs of in-patient care and outpatient visits.

4.7 Outcome measures

Several measures were used to evaluate patient outcome. The most concrete and clear cut outcome is **mortality**, which is easily measured using the data from the CDR. Mortality was evaluated at several time points, both short term, i.e. 1 month, to measure effectiveness of acute care; at 1 year, to measure the effectiveness of rehabilitation, follow-up, and secondary prevention; and long-term, up to a decade, to measure the long-term effects of rehabilitation, secondary prevention, and changes in median survival of patients.

In addition to mortality, a functional outcome evaluation in the surviving patients would have been welcome, such as the widely used mRS score. However, such scores are not nationally registered, so one has to settle for a surrogate outcome measure for functional outcome. **Living status** was used for this purpose. Whether a patient was living at home at various time points after stroke, and the number of days spent home within a year from stroke were evaluated. In addition to institutional care, independence among the patients living at home would have important to know, but again, this is not registered nationally.

Mortality and need for institutional care mainly reflect the success of acute care and rehabilitation. In long term follow-up, also the success of secondary prevention is important and of interest. **Recurrences** were therefore evaluated. It is not possible to deduce possible recurrences or multiple strokes within the initial stroke in-hospital episode, as the stroke primary diagnosis could reflect either the initial stroke or a recurrence. Therefore, only new acute stroke hospitalizations were considered recurrences. In order to minimize the risk of incorrect coding, a new acute stroke episode was considered a recurrence only when:

- a) The initial stroke episode of continuous in-patient care had finished, i.e. the patient had been discharged home or to a nursing home AND
- b) Patient was admitted through the emergency room with a primary diagnosis of acute stroke AND
- c) The new episode lasted at least 3 days or lead to death before that

4.8 Benchmarking

An important aspect of the PERFECT Stroke project has been to compare providers and geographical areas with regard to performance, effectiveness, and costs. To make such comparisons meaningful, the patient case-mix have to be similar, which is usually not the case, or the differences in patient case-mix have to be adjusted for.

As there are large differences in the age distribution and prior co-morbidities of patients treated in different hospitals and different areas of Finland, adjustments were made for the

differences. As adjustments cannot take all differences in case-mix into account, such as stroke severity which is not nationally registered, the patients for comparisons were chosen in a way to make them more alike. For benchmarking purposes, only ischemic stroke patients were compared, and the following patient groups were excluded:

1. Patients younger than 18 years of age – the rare cases often treated in pediatrics
2. Non-residents – tourists and visitors cannot be reliably followed up
3. Residents of the Archipelago of Åland – the total population is small, less than 30 000 people, and these patients are sometimes treated in Sweden
4. Patients residing in a long-term institution before their stroke, defined as 90 days of continuous in-patient care prior to their stroke

The benchmarking itself was performed by adjusting for age, sex, prior co-morbidities as defined before, and the use of warfarin or statin prior to stroke. These two medications were adjusted for separately, as their indication cannot always be deduced from register data. The medications and co-morbidities were chosen by the PERFECT Stroke steering group based on possible clinical relevancy.

Annual reports of the benchmarking population, with both crude and adjusted figures for baseline demographics, LOS at various levels of care, procedures, medications prior and post stroke, costs, and outcome measures, have been produced.

Two sets of annual reports are given. In the first set, all health districts are compared with each other, to evaluate geographical differences and the success of whole chains of recovery. In the second set, all hospitals with at least 50 benchmarking population patients in the year 2003 are compared with each other, to evaluate possible provider differences in mainly acute care. For hospital comparisons, when the patient was rapidly transferred between hospitals, the highest level of care within the first week of stroke (local hospital, regional hospital, or university hospital) was considered to have been responsible for the patient care. In the beginning of year 2007, two regional hospitals (Jorvi and Peijas) were organizationally joined with the Helsinki University Central Hospital (HUCH), and all of the patients were grouped under HUCH.

The follow-up for the main outcome measures is 1 year, and the registries have to be checked, cleaned, and linked after the follow-up period. There is therefore currently a two-year lag from patient care to reports. For study III, data was available for patients with their first-ever stroke between 1st January 1999 and 31st December 2006 with follow-up of all patients until 31st December 2007. For studies I, II, and IV, data was available for patients with their first-ever stroke between 1st Jan 1999 and 31st December 2007 with follow-up of all patients until 31st December 2008, and has since become available also for patients with their first-ever stroke up to 31st December 2008 with follow-up of all patients up to 31st December 2009.

4.9 Statistical methods

Continuous data is presented as median with interquartile range, or mean with standard deviation. Categorical variables are presented as numbers and percentage of category total. Differences between multiple groups (study III) are analyzed with Kruskal-Wallis or analysis of variance methods where appropriate. In the annual reports, incidence of benchmarking ischemic stroke patients is reported as crude per 100 000 population, and as age and sex standardized to the national population of that year. For comparison of incidence in time, the data is age and sex standardized to a fixed year with the direct method.

For benchmarking purposes in the annual reports, and in studies II, III, and IV, suitable regression models are used for adjustment of baseline imbalances. Logistic regression models are used for binary outcomes (mortality, institutional care, recurrence), and generalized linear models (GZLM) with gamma distribution and log link for continuous outcomes (LOS, costs, days spent home within a year of stroke). All the models used the same covariates which were forced in to the model: age, sex, all comorbidities, and use of warfarin and statin prior to stroke. For benchmarking purposes, with the model parameter estimates, an expected probability for each outcome was calculated for each patient. The observed outcomes of patients in a hospital or health district were compared to the expected outcomes of the same patients (observed/expected) (*DeLong et al. 1997*). This proportion was multiplied by 100 to derive an index where 100 was the national average for that outcome, and the index value for each outcome described how many percentages of the national average that district or hospital had achieved after adjustment for imbalances. The index values are reported with 95% confidence intervals, calculated as described elsewhere (*Ash et al. 2003*).

For analysis of time trends in the care and outcome of patients of the whole country (study II), all first-ever IS, ICH, and SAH patients were included. The regression models were otherwise similar to the ones used in annual reports, but prior living status was adjusted for, as also previously institutionalized patients were included in the analysis. Year of stroke was introduced as a covariate to analyze possible differences over time. To test for difference in long-term outcome between patients of years 1999 and 2007, a Cox proportional hazards regression model was utilized with the same covariates.

For analysis of hospital stroke center designation effect on patient outcome (studies II and III), similar logistic and Cox regression models were utilized, with hospital classification introduced to the model. As most stroke patients in Finland are treated by neurologist, but also many by GPs or internal medicine specialist, the analysis was done separately for patients treated by neurology only (study II). To further test the independent effect of the treating specialty (study II), the same models were run with a dichotomous variable included: acute care by neurology vs. non-neurology in IS and ICH; or neurosurgery vs. non-neurosurgery in SAH.

5 RESULTS

5.1 National stroke database (Study I)

The PERFECT Stroke database includes 104 899 first-ever stroke patients for the years 1999 to 2008, of whom 82 950 (79.1%) had IS, 14 267 (13.6%) ICH, and 7682 (7.3%) SAH as their first stroke (Table 4). Men and women had almost as many strokes, but men had their strokes a decade younger than the women. The age- and sex distribution of the patients for the whole 10-year period are shown in Table 5, and the data for the years 1999 and 2008 graphically (Figure 3, Figure 4, Figure 5).

Median age was 74, with interquartile range (IQR) of 63 to 81 years. The corresponding figures among IS patients were 75 (67-82) in 1999 and 76 (65-83) in 2008; among ICH patients 72 (61-79) and 72 (61-81); and among SAH patients 54 (44-67) and 57 (48-69) respectively. Of all patients, 6313 (6.0%) were living in an institution before their stroke.

Table 4. *Number of patients by stroke subtype, years 1999 – 2008*

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
SAV	866	801	787	786	754	824	709	739	721	695
ICH	1 449	1 410	1 406	1 408	1 439	1 389	1 451	1 419	1 415	1 481
IS	8 390	8 387	8 570	8 172	8 178	8 418	8 069	8 172	8 213	8 381
Total	10 705	10 598	10 763	10 366	10 371	10 631	10 229	10 330	10 349	10 557

Table 5. *Age- and sex distribution of stroke patients, years 1999 – 2008, with cumulative percentage for age-group total.*

Age	IS		ICH		SAH		Total Stroke		Cum.%
	Male	Female	Male	Female	Male	Female	Male	Female	
0-24	116	125	93	46	81	61	290	232	0,5 %
25-34	216	196	102	58	179	157	497	411	1,4 %
35-44	837	513	285	137	537	518	1 659	1 168	4,1 %
45-54	3 355	1 596	903	477	975	1 009	5 233	3 082	12,0 %
55-64	7 854	3 681	1 657	812	820	994	10 331	5 487	27,1 %
65-74	12 116	8 947	2 055	1 521	473	760	14 644	11 228	51,7 %
75-84	11 479	17 528	1 795	2 613	254	586	13 528	20 727	84,4 %
85-94	3 374	10 195	390	1 255	60	205	3 824	11 655	99,1 %
95+	131	691	14	54	3	10	148	755	100,0 %
Total	39 478	43 472	7 294	6 973	3 382	4 300	50 154	54 745	

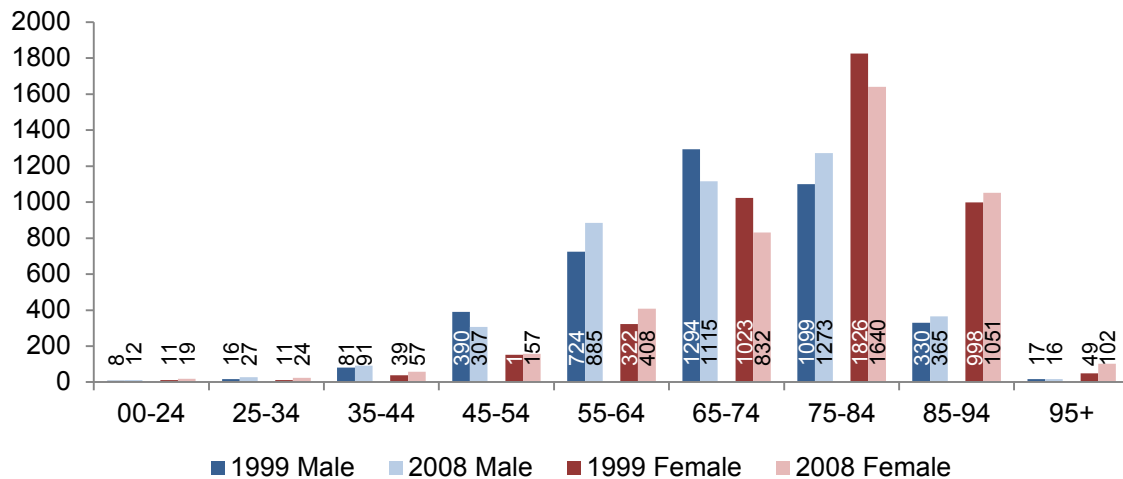


Figure 3. Age and sex distribution of IS patients, years 1999 (n=8390), 2008 (n=8381)

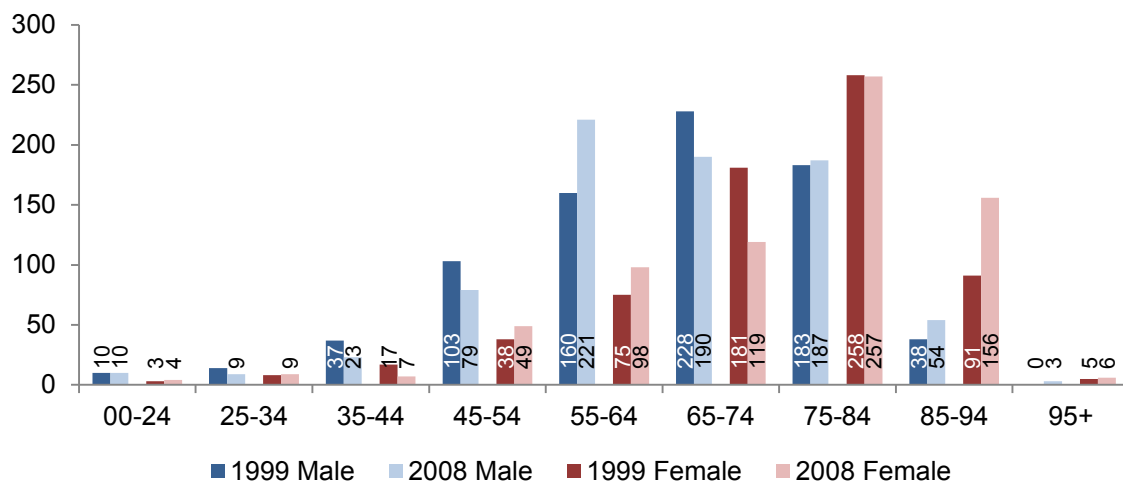


Figure 4. Age and sex distribution of ICH patients, years 1999 (n=1449), 2008 (n=1481)

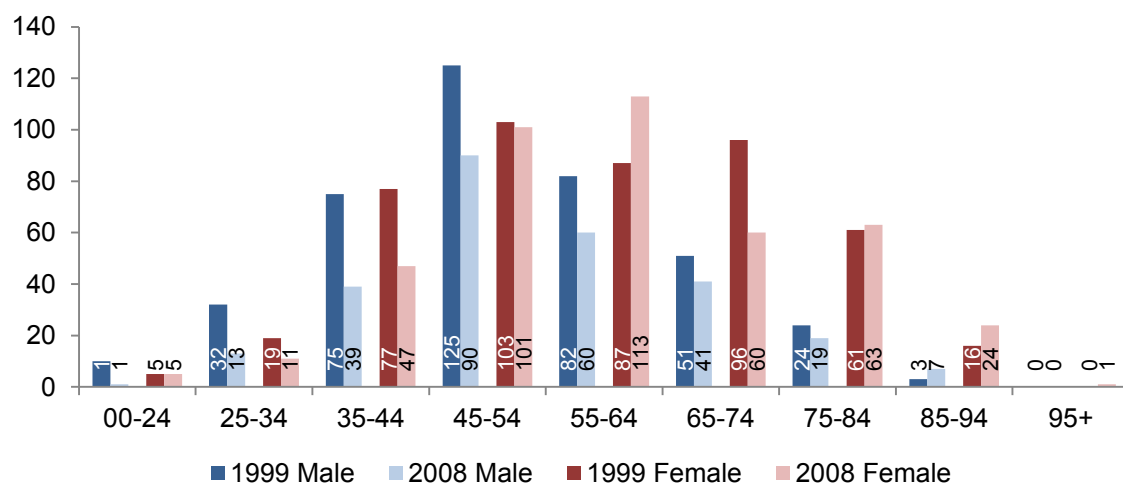


Figure 5. Age and sex distribution of SAH patients, years 1999 (n=866), 2008 (n=695)

As the incidence of stroke is clearly and strongly age-dependent, and the population of Finland is rapidly ageing over the study period (Table 6), one would expect to see more stroke cases over time. This has not been the case, mainly due to decrease in stroke incidence in the oldest patients. The total age and sex adjusted incidence fell by 18% over the study period (Table 7), most of which was due to IS patients (Table 8).

Table 6. *Age and sex distribution of the Finnish population, years 1999 and 2008.*

	1999			2008		
	Male	Female	Total	Male	Female	Total
0-24	818 744	784 529	1 603 273	791 624	758 155	1 549 779
25-34	337 911	324 102	662 013	346 247	328 244	674 491
35-44	390 473	376 952	767 425	346 410	333 645	680 055
45-54	418 501	409 510	828 011	381 504	378 146	759 650
55-64	264 616	278 796	543 412	380 565	389 706	770 271
65-74	190 450	245 333	435 783	218 156	254 691	472 847
75-84	83 782	170 547	254 329	120 859	194 565	315 424
85-94	17 955	55 793	73 748	25 213	72 459	97 672
95+	594	2 714	3 308	1 075	5 050	6 125
Total	2 523 026	2 648 276	5 171 302	2 611 653	2 714 661	5 326 314

Table 7. *First-ever all stroke incidence in the PERFECT database per 100 000 population in Finland, years 1999 and 2008, according to age and sex.*

	1999			2008			Change	95% CI
	Male	Female	Total	Male	Female	Total		
0-24	3	2	3	3	4	3	12 %	-30 55%
25-34	18	12	15	14	13	14	-9 %	-36 18%
35-44	49	35	42	44	33	39	-9 %	-24 7%
45-54	148	72	110	125	81	103	-6 %	-16 3%
55-64	365	174	267	306	159	232	-13 %	-20 -7%
65-74	826	530	659	617	397	498	-24 %	-29 -20%
75-84	1 559	1 258	1 357	1 224	1 007	1 090	-20 %	-24 -15%
85-94	2 066	1 981	2 001	1 690	1 699	1 696	-15 %	-22 -9%
95+	2 862	1 990	2 146	1 767	2 158	2 090	-3 %	-33 25%
Total	203	210	207	197	200	198	-4 %	-7 -2%
Total*				162	176	171	-18 %	-20 -15%

Change in total stroke incidence, with 95% confidence intervals (CI) calculated with the Newcombe-Wilson method without continuity correction (*Newcombe 1998*).

*Age and sex standardized with the direct method to the population of the year 1999.

Table 8. First-ever ischemic stroke incidence in the PERFECT database per 100 000 population in Finland, years 1999 and 2008, according to age and sex.

	1999			2008			Change	95% CI	
	Male	Female	Total	Male	Female	Total			
0-24	1	1	1	2	3	2	69 %	-5	99%
25-34	5	3	4	8	7	8	85 %	16	196
35-44	21	10	16	26	17	22	39 %	9	77
45-54	93	37	65	80	42	61	-7 %	-18	0%
55-64	274	115	192	233	105	168	-13 %	-20	-5%
65-74	679	417	532	511	327	412	-23 %	-27	-18%
75-84	1 312	1 071	1 150	1 053	843	924	-20 %	-24	-15%
85-94	1 838	1 789	1 801	1 448	1 450	1 450	-19 %	-25	-13%
95+	2 862	1 805	1 995	1 488	2 020	1 927	-3 %	-28	30%
Total	157	167	162	157	158	157	-3 %	-6	0
Total*				128	139	134	-17%	-20	-15%

Change in total stroke incidence, with 95% confidence intervals (CI) calculated with the Newcombe-Wilson method without continuity correction (Newcombe 1998).

*Age and sex standardized with the direct method to the population of the year 1999.

The prevalence of stroke survivors in Finland was estimated at 82 000 at the end of the year 2008, based on observational data of the patients with their stroke in the years 1999 to 2007, 50 929 patients of whom were alive at that date, and extrapolation of the patients of years 1970 to 1998, as shown in Figure 6.

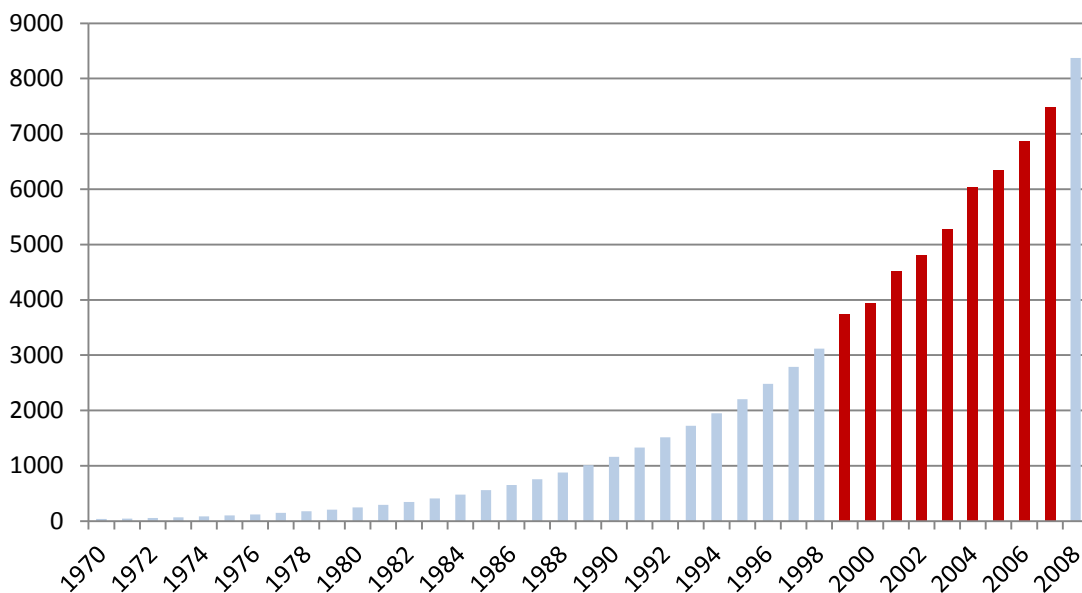


Figure 6. Patients alive at end of 2008, by year of incident stroke. Observational PERFECT-data in red, extrapolation in blue

Some comorbidities prior to stroke became more common (cancer, depression, hypertension, and COPD), and some less frequent (coronary heart disease and cardiac failure) (Table 9). All comorbidities were associated with outcome (Table 10).

Of all stroke patients, 62% were treated in stroke centers (Table 2 of Study I), and of the IS patients, 6% received thrombolytic therapy and 49% a guideline combination of secondary preventive medications (Table 2 and discussion of Study I).

Table 9. *Prior co-morbidities in stroke patients of the years 1999 and 2008.*

	IS		ICH		SAH	
	1999	2008	1999	2008	1999	2008
Hypertension	63 %	68 % **	52 %	55 %	30 %	40 % **
Coronary heart disease	29 %	26 % **	18 %	18 %	8.2 %	8.1 %
Atrial fibrillation	15 %	16 %	10 %	11 %	3.2 %	3.7 %
Cardiac failure	18 %	11 % **	12 %	7.1 % **	2.5 %	2.6 %
Peripheral artery disease	4.5 %	3.7 % *	2.5 %	2.3 %	1.0 %	1.6 %
Diabetes	19 %	19 %	11 %	14 % *	4.2 %	7.5 % *
Chronic obstructive pulmonary disease	12 %	15 % **	11 %	10 %	9.1 %	12 % *
Cancer	8.2 %	13 % **	8.4 %	11 % *	3.2 %	5.6 % *
Depression	12 %	15 % **	12 %	13 %	10 %	14 % *
Dementia	2.8 %	7.3 % **	2.6 %	8.9 % **	0.5 %	2.0 % *
Alcoholism	1.8 %	4.2 % **	4.8 %	4.7 %	4.3 %	4.6 %
Other mental disease	7.9 %	6.6 % **	7.4 %	5.6 %	4.4 %	4.5 %
Parkinsons's disease	3.1 %	4.9 % **	3.6 %	3.2 %	2.7 %	2.7 %

Chi squared test: $p < 0.05 = *$; $p < 0.001 = **$

Table 10. *Effect of comorbidities on 1-year case-fatality.*

	IS	ICH	SAH	All stroke
Age, per year	1.07 (1.07-1.08)	1.03 (1.03-1.04)	1.04 (1.04-1.04)	1.05 (1.04-1.05)
Male sex	1.06 (1.02-1.11)	1.03 (0.95-1.11)	1.04 (0.92-1.16)	0.97 (0.94-1.01)
Hypertension	1.15 (1.10-1.20)	1.15 (1.06-1.25)	1.25 (1.10-1.41)	1.05 (1.01-1.09)
Coronary heart disease	1.18 (1.13-1.23)	1.22 (1.10-1.36)	1.26 (1.03-1.53)	1.12 (1.08-1.16)
Atrial fibrillation	1.27 (1.21-1.34)	1.16 (1.01-1.34)	0.79 (0.58-1.07)	1.15 (1.10-1.20)
Cardiac failure	1.64 (1.57-1.73)	1.41 (1.22-1.62)	1.35 (0.99-1.85)	1.60 (1.53-1.67)
Peripheral artery disease	1.88 (1.74-2.04)	2.27 (1.77-2.90)	1.06 (0.68-1.65)	1.72 (1.60-1.84)
Diabetes	1.24 (1.18-1.30)	1.29 (1.15-1.45)	1.00 (0.79-1.26)	1.11 (1.07-1.16)
COPD	1.07 (1.01-1.12)	0.96 (0.85-1.09)	0.93 (0.78-1.12)	1.00 (0.95-1.04)
Cancer	1.47 (1.39-1.55)	1.84 (1.63-2.07)	1.41 (1.12-1.78)	1.52 (1.45-1.59)
Depression	1.15 (1.09-1.22)	1.08 (0.96-1.21)	1.00 (0.83-1.22)	1.14 (1.09-1.20)
Dementia	2.16 (2.01-2.32)	1.84 (1.55-2.19)	1.53 (0.95-2.46)	2.14 (2.00-2.28)
Alcoholism	1.66 (1.47-1.86)	1.22 (1.02-1.47)	1.62 (1.25-2.11)	1.53 (1.39-1.67)
Other mental disease	1.68 (1.57-1.80)	1.41 (1.21-1.64)	1.24 (0.96-1.61)	1.50 (1.42-1.59)
Parkinson's disease	1.09 (0.99-1.20)	1.17 (0.95-1.43)	1.21 (0.84-1.76)	1.10 (1.01-1.19)
Prior warfarin use	1.13 (1.06-1.20)	1.47 (1.29-1.67)	1.40 (1.04-1.89)	1.27 (1.21-1.34)
Prior statin use	0.65 (0.61-0.68)	0.70 (0.62-0.78)	0.93 (0.77-1.11)	0.64 (0.61-0.66)

Multivariate logistic regression model odds ratios with 95% confidence intervals.

5.2 Trends in stroke case-fatality (Study II)

There has been a marked decrease in the overall 1-year case-fatality of IS patients from 1999 (26.2%) to 2008 (21.6%), owing mostly to the decrease in very early deaths within 28 days of stroke, 13.0% to 10.0% respectively. A similar trend was seen among ICH patients, with 1-year case-fatality dropping from 43.0 to 40.9%, stemming exclusively from decreased 28-day mortality (32.2% to 29.3%). Among SAH patients, no clear trend was seen (Figure 7).

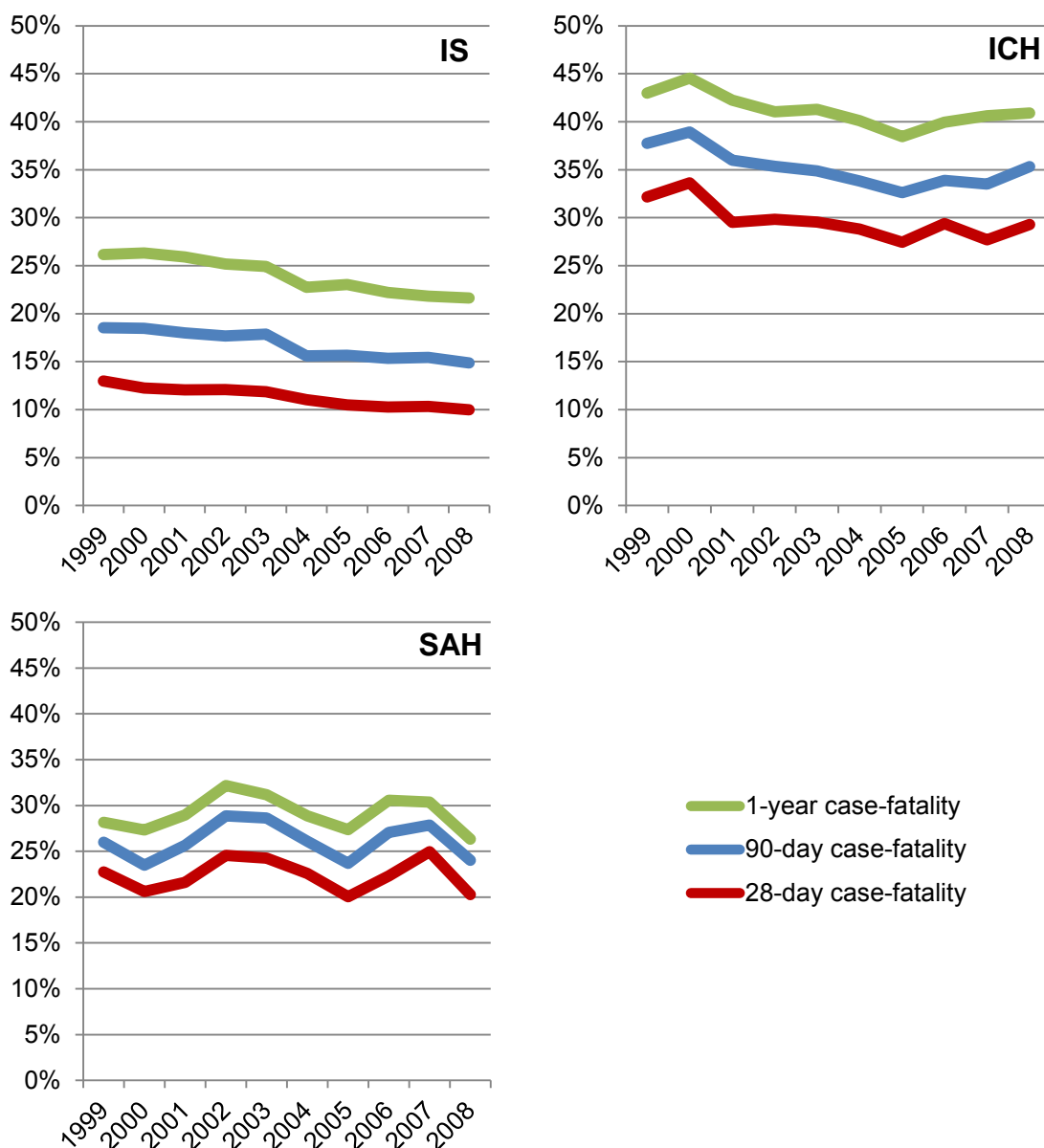


Figure 7. Crude trends in case-fatality by stroke subtype, years 1999 to 2008.

The decrease in case-fatality has led to increased life-expectancy after stroke. After adjusting for patient characteristics, the median survival after IS has increased by 2 years, and after ICH by 1 year over the study period (Figure 4 of Study II).

The proportion of patients treated at stroke centers and by neurologists increased steadily over the study period, and this centralization and specialization of care was associated with increased patient survival (Study II). After adjusting for patient case-mix, treatment by neurologists was associated with increased 1-year survival among IS (OR 1.77; 1.70-1.84) and ICH-patients (OR 1.54; 1.40-1.69) when compared to treatment by any other specialty. Treatment by neurosurgeons was likewise associated with increased 1-year survival in SAH patients (OR 2.66; 2.25-3.16).

5.3 Stroke centers (Study III)

The last audit of facilities and processes of hospitals treating stroke in Finland was performed in the year 2006. Thus the effect of stroke centers on patient outcome was analyzed in the patients of the years 1999 to 2006. Only ischemic stroke was analyzed in study III, and exclusions were done as in the annual PERFECT Stroke reports. The total number of patients in this analysis was 61 685. Of these patients, half were treated in general hospitals (GH, $n = 30\,891$), 17% in primary stroke centers (PSC, $n = 10\,749$), and 32% in comprehensive stroke centers, (CSC, $n = 20\,045$). In the year 2006, there were 7 hospitals fulfilling PSC and 5 hospitals fulfilling CSC criteria in Finland.

All-cause case-fatality within 1 year of stroke was 27.3 % in GHs, 19.1% in PSCs, and 16.6% in CSCs. There were major imbalances in baseline characteristics of the patients treated in the various hospitals. After adjusting for these, the risk of death within 1 year of stroke in patients treated in GHs was 23.2% (95% CI 22.8–23.6%), in patients treated in PSCs 21.7% (20.9–22.5%), and in patients treated in CSCs 20.8% (20.2–21.5%). The number-needed-to-treat (NNT) to allow 1 more patient to live at home 1 year from stroke was 29 (23–38) for CSCs, 40 (28–68) for PSCs, and 32 (26–42) for stroke center combined when compared with GHs. The difference between PSC and CSC was not statistically significant, NNT 100 (50– -1100).

After publication of study III, concerns were raised whether the stroke center effect was due to treating specialty, not due to stroke center facilities. This was tested in study II, where the analysis was now restricted to patients treated by neurologists (69% of all IS patients) in either GH or a stroke center. The effect of stroke center care on 1-year case-fatality was in this analysis smaller (OR 0.94; 0.89– 0.99; $p=0.022$) than in the whole population (OR 0.79; 0.76–0.82; $p<0.001$). Similarly, a smaller but still positive effect of stroke centers was seen when the analysis was restricted to patients treated in neurology, in the 1-year outcome of death or institutional care (OR 0.91; 0.88–0.96; $p<0.001$) vs. (OR 0.76; 0.74–0.79; $p<0.001$) in the whole population.

In study II, the effectiveness of stroke center treatment on ICH patient 1-year mortality among patients treated by neurologist (65% of all ICH patients) was also tested, and an effect just barely significant could be realized for patients treated in CSC (OR 0.90; 0.80–1.00; $p=0.05$), but in the opposite direction among patients treated in PSCs (OR 1.13; 1.00–1.29; $p=0.06$), when compared to GHs. Together, the stroke centers reduce the risk of death or institutional care after ICH only in a non-significant manner (0.92; 0.83–1.01; $p=0.1$) as compared to general hospitals.

5.4 Costs of stroke (Study IV)

Study IV was published in an American journal and the results were therefore reported in US dollars. Since then, the data of year 2008 has become available. The mean total 1-year cost of stroke patients in the year 2008, in 2008 values, was 20 446 € (median 10 875 €; IQR 5 041–25 218 €), 19 252 € (10 358 €; 5056–23 245 €) in IS patients, 23 873 € (12 739 €; 4 352–32 641 €) in ICH patients, and 27 538 € (17 129 €; 6 366–36 230 €) in SAH patients. Costs in IS patients increased with age, but decreased in older ICH and SAH patients, mostly reflecting high case-fatality rates in the older hemorrhagic stroke patients (Table 11).

The costs of stroke patients are primarily in-patient costs, while outpatient visits and medication costs form a minor portion. Absolute 1-year costs have increased during the last 10 years by 54% for total stroke, 48% for IS, 74% for ICH, and 84% for SAH patients. Cost of stroke care has increased more than healthcare costs in general, as during the same period the hospital cost index (www.stat.fi) has increased by 35% only (Figure 8). This development may have stopped, as stroke 1-year costs have increased from 2006 to 2007 (3.0%) and 2007 to 2008 (1.6%) less than the healthcare cost index, 3.3% and 5.6% respectively.

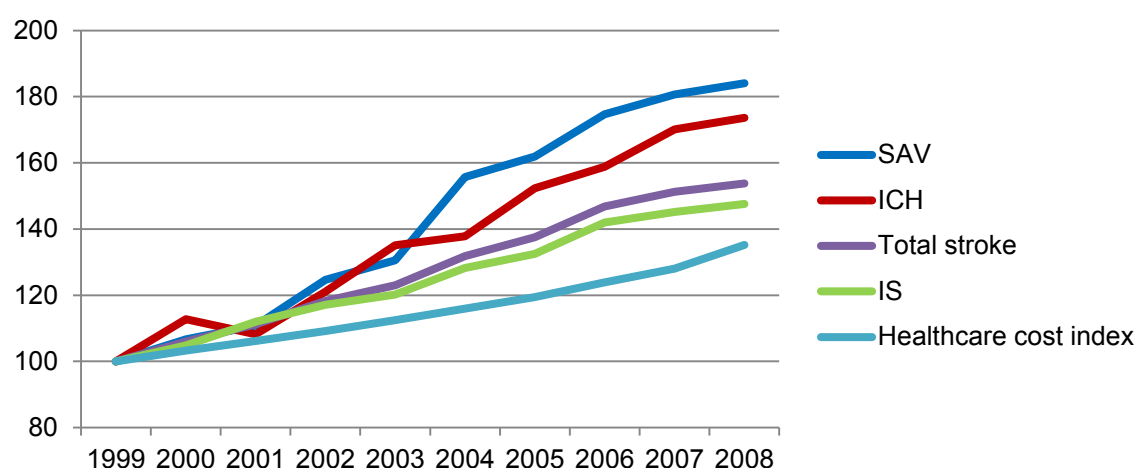


Figure 8. Crude mean 1-year cost of stroke and the healthcare cost index, year 1999 = 100.

The mean lifetime direct healthcare costs of a patient after stroke were estimated at 86 300 €, or 88 900 € after IS, 87 600 € after ICH, and 55 400 € after SAH.

The 1-year costs directly attributable to stroke, when the mean daily cost prior to stroke was subtracted from each day the patient survived, were 82% of total cost, or 79% in IS, 89% in ICH, and 93% in SAH patients. Similarly, the lifetime costs directly attributable to stroke were 56 400 € (65% of all lifetime costs), or 55 900 € (63%) in IS, 65 700 € (75%) in ICH, and 43 800 € (79%) in SAH patients.

The total cost of treating stroke patients in Finland is about 1.1 € Billion annually, 7% of total healthcare costs, or 0.6% of GDP (Study IV).

Table 11. *Total healthcare costs within 1 year of stroke by age and sex, year 2008, €.*

Male		00-24	25-34	35-44	45-54	55-64	65-74	75-84	85-94	95+	Total
IS	<i>n</i>	12	27	91	307	885	1 115	1 273	365	16	4 091
	Mean	14 574	22 701	15 586	14 932	15 818	17 521	19 640	21 770	27 081	18 017
	SD	11 696	41 675	23 719	21 248	21 043	20 983	23 952	24 065	49 068	22 727
	Median	9 503	6 365	6 627	7 986	8 319	10 045	11 371	13 130	7 222	9 891
	Percentile 25	5 624	3 357	4 595	4 324	4 402	4 910	5 419	5 621	5 576	4 891
	Percentile 75	25 242	20 517	13 081	16 229	17 836	21 476	23 094	29 527	17 431	21 248
ICH	<i>n</i>	10	9	23	79	221	190	187	54	3	776
	Mean	17 344	40 709	18 748	31 675	23 598	26 052	23 180	16 248	11 774	24 337
	SD	14 759	40 372	19 618	37 046	31 251	30 380	30 784	20 506	15 962	30 726
	Median	14 060	27 109	12 354	19 430	12 905	15 216	12 373	7 774	3 131	13 245
	Percentile 25	2 653	12 370	4 826	6 270	4 431	5 483	3 730	2 132	1 998	4 560
	Percentile 75	28 661	39 141	24 384	38 785	30 173	35 494	31 395	18 932	30 194	32 092
SAV	<i>n</i>	1	13	39	90	60	41	19	7	0	270
	Mean	1 564	35 677	24 870	28 277	27 810	19 743	16 347	17 473		25 523
	SD		36 864	31 842	30 514	27 943	21 574	16 993	35 575		28 697
	Median	1 564	22 862	13 407	15 143	18 998	13 945	7 656	3 591		15 007
	Percentile 25	1 564	15 028	5 296	8 381	7 932	5 057	5 430	460		6 193
	Percentile 75	1 564	44 158	32 716	39 340	38 848	24 233	34 999	9 802		35 645
Female		00-24	25-34	35-44	45-54	55-64	65-74	75-84	85-94	95+	Total
IS	<i>n</i>	19	24	57	157	408	832	1 640	1 051	102	4 290
	Mean	37 126	17 531	15 608	15 129	15 420	18 361	21 977	22 465	19 922	20 430
	SD	96 228	20 863	16 511	18 942	20 179	24 439	28 579	25 341	27 556	26 592
	Median	9 332	7 723	7 677	7 234	8 365	9 239	12 239	13 279	9 702	10 858
	Percentile 25	4 527	6 645	4 585	4 025	4 183	4 771	5 745	5 977	5 517	5 259
	Percentile 75	15 307	23 773	20 531	18 055	16 292	22 742	27 553	29 984	24 111	25 674
ICH	<i>n</i>	4	9	7	49	98	119	257	156	6	705
	Mean	29 897	28 439	29 956	22 191	24 439	25 928	24 631	18 623	13 694	23 363
	SD	28 365	39 342	33 705	21 294	31 555	29 858	31 457	21 876	14 411	28 699
	Median	27 455	10 127	18 349	17 515	13 445	12 739	12 261	9 338	7 979	12 013
	Percentile 25	6 414	8 807	4 860	4 138	4 334	5 015	4 654	1 865	1 672	4 061
	Percentile 75	53 380	19 736	73 017	30 246	34 051	40 467	31 573	27 417	30 681	33 606
SAV	<i>n</i>	5	11	47	101	113	60	63	24	1	425
	Mean	15 145	17 810	21 276	32 736	31 233	32 872	28 038	16 656	1 752	28 818
	SD	13 561	14 725	18 288	37 091	33 819	34 008	40 089	19 982		33 417
	Median	18 845	17 129	15 583	20 070	20 639	22 662	16 072	8 838	1 752	18 037
	Percentile 25	2 734	6 031	8 616	8 989	8 618	7 247	4 431	2 905	1 752	6 842
	Percentile 75	18 848	18 771	27 360	35 397	39 514	48 864	36 294	29 567	1 752	36 294

6 DISCUSSION

In this study, a national stroke database was created using linkage of existing administrative registries. This method does not require extra data collection or input, and is therefore inexpensive and easy to maintain over long periods of time. Data for the first 10 years show improvements in care of patients revealed by increased survival and less institutional care after stroke. Specialized and centralized care is associated with this improvement, and the effectiveness of stroke center care was shown for the first time anywhere in the world, with nationwide data for the whole population.

The life-time direct healthcare costs of stroke patients are high, on average ~86 000 € from stroke until death, but a third of these are attributable to other concomitant diseases. The prevalence of stroke in Finland is about 82 000, 1.5% of national population, and these patients incur an annual healthcare cost of about 1.1 Billion €, 0.6% of the national GDP.

Only 62% of stroke patients have been treated in stroke centers, which is four times higher than in Europe in general (*Leys et al. 2007a*), but still not satisfactory. Of IS patients, only 6% received thrombolytic therapy and only 49% a combination of secondary preventive medications as suggested by national guidelines. Treatment of stroke is demanding and requires know-how and motivation. There is much room for improvement, and such improvements could have national economic impact.

6.1 Main results in light of existing literature

National stroke databases

Several previous national stroke databases exist. These have been reviewed, compared with the PERFECT Stroke, and published earlier (Table 3 of Study I).

The first and most comprehensive is the Swedish RIKS Stroke, with prospective registration of patients since 1994 (*Stegmayr et al. 1999; Asplund et al. 2003; Appelros et al. 2007*), about 80% of national patients registered, with extensive follow-up including a functional outcome measure at 3 months (*Eriksson et al. 2007*). Many of the elements registered in RIKS Stroke are identical to PERFECT Stroke: Prior place of living; comorbidities; medications before and after stroke; LOS and episode of care data; diagnosis; and in-hospital mortality. In addition, RIKS Stroke includes data on functional status (home-help, mobility, toilet visits, and dressing) before and after stroke; smoking status; information on whether a CT, MRI, or ultrasound was performed; information on complications; patient satisfaction; and most importantly, level of consciousness and NIHSS on arrival (*Riks-Stroke Collaboration 2011*). Thrombolytic therapy is included in the PERFECT database as a simple yes/no parameter, with some more detail in the RIKS Stroke, but to be really able to analyze this special therapy, more detail is needed, such as with the SITS registry (*Wahlgren et al. 2007*) currently used in both Finland and Sweden.

Although long-term follow-up and medication use data is not included in the RIKS Stroke registry, for research purposes it is possible to link this data (*Eriksson et al. 2008; Asberg et al. 2010*) in a similar fashion as has been done with PERFECT. Thus RIKS Stroke is a model example of a national stroke registry.

A second database with full nationwide coverage is the Scottish Stroke Care Audit (SSCA, available at www.strokeaudit.scot.nhs.uk), which, just like PERFECT and RIKS Stroke, has been mainly hospital-based, and due to a large portion of patients treated as outpatients in Scotland, includes about 60% of national patients (*Dennis et al. 2009*). However, stroke clinics are currently also registering patients, likely to increase the coverage. The national reports are excellent in illustrating differences among providers and pinpointing improvement areas for clinical practice (*Dennis et al. 2010*). Long-term follow-up is not included in the SSCA and register linkage is more difficult to achieve in Scotland than in Sweden or Finland.

In the USA there are two national projects for registering stroke patients, namely the Paul Coverdell National Acute Stroke registry (*George et al. 2009*), and the Get With The Guidelines (GWTG) registry run by American Heart Association (AHA) (*LaBresh et al. 2008*). The former has been less popular and slower to spread nationwide, with 56,969 patients registered from 2005 to 2007 and only few scientific publications on these. The latter has registered 1 million patients between 2003 and 2009 (*Fonarow et al. 2010*) and participation has been shown to improve patient outcome (*Schwamm et al. 2009*).

Change in incidence

PERFECT Stroke is not a true incidence study, with only hospital-based patient catchment. If the PERFECT data is used as a surrogate for incidence, the age-standardized decline in stroke incidence, reported at 2.0% annually over the years 1982 to 1998, has continued at a similar rate since, 1.8% annually over the years 1999 to 2008 (Table 7). In the younger IS patients below 45 year of age, this could not be seen (Table 8), with a slight increase instead, but the total numbers of these young patients were very small, only 4% of all patients (Table 5, Figure 3). The total age and sex standardized incidence fell by 18% (95% CI 15% to 20%) from 1999 to 2008. The positive trend reported since 1972 (*Tuomilehto et al. 1993; Numminen et al. 1996; Sivenius et al. 2004; Pajunen et al. 2005*) continues.

Stroke incidence has been studied in several studies over the last decades. When the PERFECT data is compared to these, the incidence rates are lower (Figure 9). This is natural, as patients who died before hospital admission, were treated as outpatients, or had an undetermined stroke were excluded from PERFECT. The CVDR database (*Laatikainen et al. 2004*) uses similar methodology and the same primary data sources as the PERFECT Stroke study, but there are significant difference in total numbers of annual patients (around 13 500 and 10 500 respectively). This is explained by different methodology. The CVDR registry contains non-traumatic epidural and subdural hematomas, which are normally not considered stroke, recurrent cases of stroke when there is 7 years between

the two strokes, which are not true first-ever strokes, and the cases of stroke which are fatal before hospitalization, which are true first-ever cases. The PERFECT database does not contain epidural or subdural hemorrhage patients, or patients with any previous stroke, checked for since 1987, but it does not either contain the true first-ever cases which were fatal before hospital admission. Also other differences exist. On the other hand the PERFECT database contain venous IS, usually considered stroke, and the diagnoses of stroke syndromes of the ICD-10 code G46, neither of which are included in the CVDR. Neither database contains the non-fatal stroke treated totally as outpatients. The true total number of annual incident stroke cases in Finland is likely to be somewhere in between the 10 500 of the PERFECT database, and the 13 500 of the CVDR database.

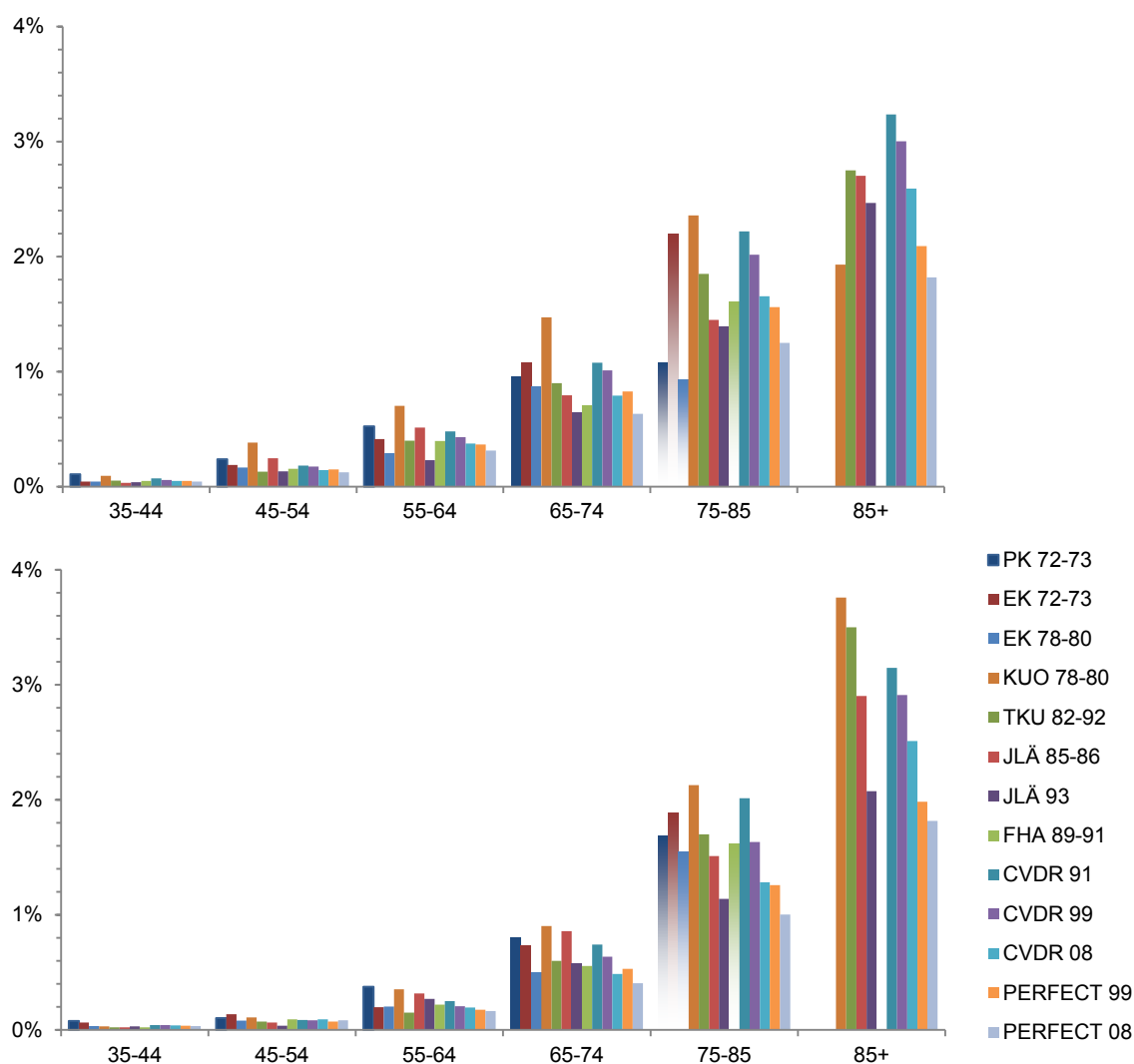


Figure 9. Finnish stroke incidence in men (top panel) and women (bottom panel) by age, percentage of population. PK, EK, and FHA studies did not separate the 85+ age-group. Abbreviations: PK, Pohjois-Karjala; EK, Espoo-Kauniainen; KUO, Kuopio; TKU, Turku; JLÄ, Jyväskylä; FHA, Finnish Heart Association; CVDR, Cardiovascular Disease Registry. For references, please see chapter 2.2.2.

Stroke prevalence has been estimated at 41 000 (0.8% of population) 20 years ago (*Rissanen 1992; Kaste et al. 2006*), 60 000 (1.2% of population) 10 years ago (*Aromaa and Koskinen 2004*), and at 82 000 (1.5% of population) currently (Study I), which is a logical continuum with decreasing case-fatality.

Comorbidities

Comorbidities were common (Table 9), and their occurrence in the first-ever stroke patients were judged to be believable. All the comorbidities that the PERFECT Stroke steering group thought might influence patient outcome, did influence it (Table 10). Statin therapy prior to stroke was associated with decreased mortality, as has been shown before (*Elkind et al. 2005; Reeves et al. 2008*).

Stroke centers

Stroke unit effectiveness has been proven in numerous studies, but these units were defined in very broad terms (*Stroke Unit Trialists' Collaboration 2007*). More strict, detailed, and intensive stroke center designation criteria have been available for a decade, but no effect of stroke center care on patient outcome has been shown before Study III. Our results have since been replicated in New York (*Xian et al. 2011*), where in a population of 30 947 stroke patients, a 3.0% (95% CI 1.5-4.4%) decrease in 1-year mortality was shown after adjustment for, in addition to age, sex, and comorbidities, also race, insurance status, rural status, hospital teaching status, and size. The crude 1-year mortality was 22.3% in stroke centers, and 26.0% in non-designated centers. This study did not analyze PSC and CSC individually, but their NNT to prevent one death at one year of 33 (95% CI 23-67) was little lower, but in the same range as ours, 42 (32-60) for CSC, and 67 (42-172) for PSC, which combined for stroke centers equals 48 (36-70). This could mean that in Finland the difference between hospitals could be lower, and the level of care in general hospitals could be higher than in New York.

While the effectiveness of stroke centers may have been expected, the results on ICH patient outcome were less intuitive. ICH patients were included in stroke unit trials, which altogether were positive, but no effect on ICH patients alone has been reported in those trials (*Stroke Unit Trialists' Collaboration 2007*). In Study II, a barely positive effect was seen for patients treated in comprehensive stroke centers, i.e. the five university hospitals in Finland, but not for PCS patients. Either a PSC standalone stroke unit, without the neurosurgical possibilities associated with CSC, is not enough for ICH patients, or there were confounders we could not control for, such as stroke severity, which explains the results.

Treating specialty

Treatment of IS and ICH patients in departments of neurology was superior to treatment by any other specialty in increasing 1-year survival, after adjustment for patient case-mix (Study II). The results are in concordance with a previous randomized trial performed in Finland in the 1980's, where treatment by neurologists as compared to internal medicine specialists improved the patient's functional status (*Kaste et al. 1995*). The fact that SAH

patients treated at a department of neurosurgery fared better than those treated at any other specialty has not been studied before in Finland.

Cost

No previous cost study on stroke has been performed with individual patient data on a population level of a whole nation (*Luengo-Fernandez et al. 2009*). A mean 1-year cost of patients who had their first stroke in Finland in the year 2008 were shown to be 20 400 €, and the lifetime costs were estimated to be 86 300 € (Study IV). The lifetime cost are somewhat higher than has been previously reported in Finland and elsewhere, when all studies are converted to year 2008 value with each country's consumer price index (available at <http://stats.oecd.org>) and then to Euros with the exchange rate of 1.47 US\$/€ (Table 12). The difference could be partly explained by increased survival of patients, as patient survival was a strong driver of total costs (Table of Study IV).

Table 12. *Lifetime cost of stroke patients in previous literature and the current study.*

Study	Years of patients	Future cost discount rate	IS	ICH	SAH	All stroke
Sweden (<i>Taylor et al. 1996</i>)	1990	5%	49 300 €	37 000 €	68 400 €	49 300 €
Sweden (<i>Terént et al. 1994</i>)	1983-1984	5%	-	-	-	69 300 €
Finland (<i>Kaste et al. 1998</i>)	1985-1989	5%				54 000 €
Netherlands (<i>Bergman et al. 1995</i>)	1991	0%	42 900 €	26 000 €	-	40 900 €
Australia (<i>Dewey et al. 2003</i>)	1996-1997	5%	29 900 €	52 300 €	-	31 700 €
Australia (<i>Cadilhac et al. 2009</i>)	1996-1997	3%	44 200 €	37 300 €	-	-
Germany (<i>Kolominsky-Rabas et al. 2006</i>)	1994-2004	3%	-	-	-	46 600 €
Present study <i>attributable cost</i>	2003	5%	88 900 € 55 900 €	87 600 € 65 700 €	55 400 € 43 800 €	86 300 € 56 400 €

All costs in 2008 values with corresponding consumer price indices, and Euros with rate 1.47 \$/€.

The total annual direct healthcare costs of all stroke survivors, 1.1 Billion €, equals about 7% of all healthcare expenditure in Finland. This estimate is slightly higher than the earlier estimate based on 1980's data from the Jyväskylä region, 6.1% (*Fogelholm et al. 2001*). The costs of treating stroke patients have increased more than healthcare costs in general especially with hemorrhagic strokes (Figure 8). This reflects two things. First,

increased survival automatically increases costs, as the dead patients are the least expensive (Study IV). Second, survival after ICH has increased, but unfortunately many of the survivors end up in institutional care, and are not able to return home (Study II). Stroke patients in long-term institutional care are the most expensive, costing about 70 000 € over the first year since their stroke (Study IV).

6.2 Study limitations

Despite its name, this database is far from perfect. The registers which supply the data also limit what can be utilized. Only those data elements which are nationally registered could be included. Also, the PERFECT Stroke database may contain some patients who did not truly have an acute stroke, may have missed some patients who did have a stroke, and certainly does lack data on many critical aspects of stroke process, patient care, costs, and outcome. The two major limitations of the present study are missing data on stroke baseline severity, and functional outcome at one year.

Specificity for including only stroke patients

The information that can be derived from the data is only as good as the quality of the data. The quality of the hospital discharge register and the causes of death register with regard to stroke have been evaluated in three studies (*Leppälä et al. 1999b; Mähönen et al. 2000; Tolonen et al. 2007*). The first study, during both ICD-8 and ICD-9 coding, included 546 middle-aged men from an alfatocopherol and beta-carotein trial over the years 1985 to 1992, where a CT, MRI, lumbar puncture, surgery, or autopsy was performed in 86% of stroke patients. Of stroke diagnoses in the HILMO, 90% were truly strokes, a further 3% were TIA or other cerebrovascular disease, and in 7% a cerebrovascular diagnosis could not be confirmed (*Leppälä et al. 1999b*).

The second study compared the HILMO and CDR with the FINMONICA Stroke registry over the years 1983 to 1994, and reported a 90% sensitivity and specificity of stroke diagnoses, but the paper is somewhat unclear on the methodology, does not report HILMO values separately from CDR values, and is thus difficult to interpret (*Mähönen et al. 2000*). At that time, the validity of the HILMO diagnoses were higher than in Sweden, where the specificity of stroke diagnoses in the hospital discharge were less than 70% (*Stegmayr and Asplund 1992*).

The most recent and relevant validation study was performed over the years 1993 to 1998, and thus, since 1996, included also the ICD-10 version stroke classification (*Tolonen et al. 2007*). The HILMO and CDR were compared to the FINSTROKE registry, and unlike the two previous validation studies, had no upper age limit. Of all first-ever acute stroke diagnoses in the administrative registries, as used in the PERFECT Stroke database (I60 SAH, I61 ICH, and I63 IS, n=3061), 93% were acute stroke (n=2838), 1% were old stroke, and 6% (n=182) were “non-stroke”. Later in the article they report, that 17% of the patients referred to as “non-stroke”, actually were acute stroke patients, just missed by FINSTROKE. Based on this data, the stroke diagnosis should be valid in 94% of cases, and a majority of the rest of the patients are probably TIA-patients. As TIA vs. stroke diagnostic criteria are evolving (FINSTROKE did not register TIA-patients, and used the time-based 24h criteria instead of a tissue-based criteria), the specificity of 94% may be an underestimation. Still, up to 6% of the patients included in the PERFECT database may actually not be acute strokes.

Sensitivity for including all stroke patients

In the same article, using FINSTROKE as the golden standard, Tolonen and colleagues report that only 2% of stroke patients in Finland were treated outside of hospitals. This tradition of treating all stroke cases as in-patients has been strong in Finland even during the first population-based incidence studies in early 1970's, with 89% hospitalization rate reported by Aho (*Aho and Fogelholm 1974*), increasing to 95% in the late 1970's (*Kotila 1986*), and later in the 1980's further to 95-97% (*Mähönen et al. 2000*). The hospital discharge register is therefore likely to include almost all stroke patients. However, many of the acute stroke patients are not coded as acute stroke, but rather by some other diagnosis, such as TIA, or a stroke syndrome (ICD-10 code G46). The sensitivity to catch all stroke patients with the ICD-10 codes I60, I61, and I63 was only 86% when compared to FINSTROKE (*Tolonen et al. 2007*). With the G46 codes it is therefore likely that about 90% of all Finnish stroke patients are included in the PERFECT Stroke registry, missing outpatients, deaths before hospitalization, and incorrect coding.

Insufficient coding of complications and procedures

The PERFECT Stroke database does contain data on complications, but these are based on entering secondary diagnoses into HILMO, which, like the primary diagnosis, are not compulsory, and where coding activity varies between hospitals. The data has been judged unreliable by the steering group, and is not included in the annual reports. Complications are not insignificant, as they may deprive stroke patients on average two year of life (*Hong et al. 2010*).

When compared to the SITS registry of thrombolytic therapies for stroke (*Wahlgren et al. 2007*), where Finland had the highest rates of thrombolytic therapies per population among European countries, the coding of thrombolytic therapy in HILMO has been judged poor (Study I). This is possibly due to the procedure being still relatively new, not being compensated in all hospital districts, but also because neurology is a conservative specialty and is not used to coding procedures. Surgeons are used to coding a procedure for almost every patient, and accordingly the rates of carotid endarterectomy have been evaluated as reliable.

Missing data elements

The most important limitation of the PERFECT Stroke database is the missing data on stroke severity. In an extensively detailed local thrombolysis register (*Meretoja et al. 2010b*), stroke severity was a more important determinant of patient 3-month outcome than age, sex, and all comorbidities put together (unpublished data). In this aspect, conventional stroke registries are superior. On the other hand, measuring stroke severity reliably requires training and certification of physicians, is not quick or easy even in experienced centers, is not comprehensively registered even in the most established national stroke register in Sweden, and is likely to form a selection bias when only stroke-oriented centers do register this. In Finland, we have considered the aspect of trying to train and certify all physicians involved in the treatment of acute stroke patients on the use

of the NIHSS (*Lyden et al. 1994*), and we do believe the project would quite likely fail. A more simple evaluation of stroke severity has been implemented and validated in Scotland, and may be one future option (*Weir and Dennis 2001; Weir et al. 2003*).

In addition to stroke severity, a major drawback of this database is the lack of information on in-hospital processes, which could be quite useful in quality improvement, such as:

- How many patients were imaged with CT / MRI on admission and during hospital stay?
- How many IS patients received ASA within 24 h of admission?
- How many patients received evaluation by occupational / speech / physiotherapist / neuropsychologist, and early rehabilitation?
- How many patients were given advice on lifestyle modification?

Information on ASA use after stroke would be useful, although the national guidelines suggest this use in combination with dipyridamole. Dipyridamole use can be currently tracked, as can be the use of clopidogrel and warfarin.

Functional outcome measured by the mRS at 3 months after stroke has become the golden standard of outcomes in stroke trials. Evaluating for this in all stroke patients is not easy to accomplish. To do this reliably asks for training and certification of the assessor. A validated functional outcome based mainly on self-reporting has been accomplished in the Swedish national registry (*Eriksson et al. 2007; Eriksson et al. 2008*), and is therefore feasible. With PERFECT Stroke, only mortality and institutional care can be measured at three months. Among other details registered in existing national registries, but missing in the present one are: smoking status, level of consciousness at arrival, complications registered prospectively, and patient satisfaction. Recurrences can be evaluated with PERFECT data, but new strokes are known to be less well coded than first-ever strokes, could be subject to error, and must be validated. Furthermore, depression and cognitive decline after the first-ever stroke can only be evaluated indirectly, based on the medications bought by the patient.

Cost data was missing for public general practice outpatient visits, home modifications, outpatient nursing, and other community help of patients living at home.

Sources of error in the models

Modeling was used to analyze the independent effect of stroke centers and treating specialty on patient outcome. Such models may be erroneous when very many variables are included at random, a situation called overmodeling. Overmodeling is a problem in small series, but with the numbers involved in the present study is not a real risk. Using the rule of 1 per 10, meaning that for each 10 outcomes, 1 factor can be considered for the model, we could have included hundreds of variables. Multicollinearity was not an issue in the models. Logistic regression models should only include variables which are

independent of each other and, in the case of continuous variables, normally distributed. Age was the only continuous variable in the logistic models, while not quite normally distributed, still close to it (Figure 10).

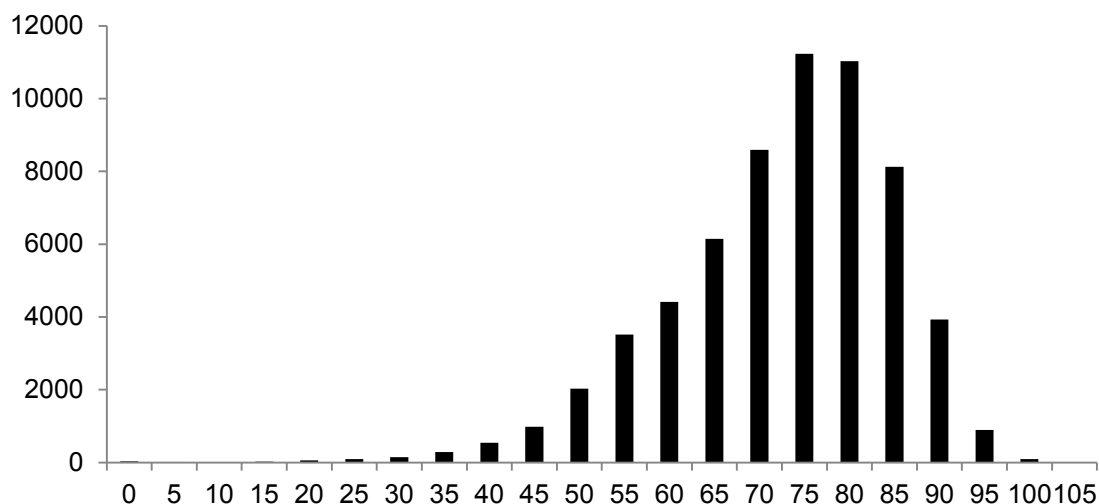


Figure 10. *Distribution of age in ischemic stroke patients.*

For estimates of prevalence, future lifetime costs, and national total costs, extrapolations had to be made. For future costs, current case-fatality rate was assumed, and the steady development of costs over the years 2 to 5 after stroke, as shown in Figure 4 of Study IV, was assumed to continue. For prevalence, we extrapolated the trends in first year case-fatality rates observed over years 1999 to 2007 (28.6% to 24.9%, thus decrease of 0.56% per year) backwards to year 1970. This implied a 1-year case-fatality of 34% in 1990 and 39% in 1980. The extrapolation based totally on PERFECT data could be correct, as Mervi Kotila reported a 1-year case-fatality rate of 39.4% in the years 1978-1980 (*Kotila 1986*), and Heikki Numminen a 1-year case-fatality rate of 34.1 % in the years 1989-1991 (*Numminen et al. 1996*). Likewise, the annual case-fatality, observed to be stable annually after first year since stroke at around 8% in patients of 1999 and 7% in patients of 2006, was extrapolated to be around 11% in the patients of 1980. No Finnish comparison data for this later extrapolation exists.

Delay in producing annual reports

The PERFECT Stroke study has looked at most of its outcome measures with 1-year follow-up. This means that it takes a full year waiting for outcomes, more than half a year for the mortality outcomes to be fully registered thereafter (Statistics Finland personnel, personal communication) due to possible autopsies and delays in death certificates, and a few more months for the registers to be linked and the reports to be published. Therefore, the reports for year 2008 patients are produced a full 2 years after end of 2008. This is considered as a too long delay to measure changes in clinical practice when one wants to use the data in improvement of processes here and now.

Strengths

In addition to the limitations mentioned above, in this study there are obvious strengths also. A lot of information has been gathered on stroke in Finland. With more than 10 000 patients registered annually, for over 10 years, and using uniform methods, clear trends in treatment and outcome of patients could be seen. The large numbers reduced the error in these estimates. With full nationwide coverage, selection bias could be reduced, which is otherwise inherent in stroke registries with voluntary participation, usually over-presenting centers with special interest and expertise in stroke care. A second strength of the registry is in the comprehensive long-term follow-up. Follow-up for case-fatality was 100%, as all national deaths were included, and also deaths occurring outside of Finland are registered. For institutional care it is possible that a few patients could have moved abroad, and were living in institutional care there, which would not be registered in PERFECT Stroke. However, it is unlikely that severely affected patients would emigrate, and according to Statistics Finland (www.stat.fi) emigration in the elderly is rare altogether, less than 0.05% annually in the over 70-year olds, so follow-up for institutional care is likely to be better than 99.9%. Full nationwide coverage and long-term follow-up are unique to this study among national registries (Table 3 of Study I), although achievable elsewhere with similar methodology.

6.3 Implications for practice and future research

The PERFECT Stroke database offers a wealth of data for research with over 100 000 patients, full nationwide coverage, 100% follow-up for institutional care and mortality, and more than 10 years of follow-up. In addition to reports for benchmarking and quality improvement, the initial purpose of the database, also research on aspects of stroke that could be nationally and internationally interesting can be done.

A paper on treatment practices in secondary prevention is under preparation, although not quite novel (*Asberg et al. 2010; Menon et al. 2010*). Also a deeper analysis of long-term costs in special patient groups, and an evaluation of indirect costs currently incurred by stroke in Finland could be meaningful to perform. The material is also especially useful for cost-effectiveness analyses, with cost and outcome data from the same patients, thus avoiding selection bias and the problem of multiple possible data sources involved in most cost-effectiveness analyses (*Earnshaw et al. 2009; Guilhaume et al. 2010*). An analysis of cost-effectiveness of secondary preventive medications has been performed, but not yet published (*Meretoja 2009; Meretoja et al. 2009*). Publication of the cost-effectiveness of the current concept of stroke centers could be analyzed and reported in detail, in order to promote a higher access to stroke care in Finland and around the world.

Another branch of future research will be in international comparisons, with the extension of the methodology to other countries, where high quality administrative registries exists, with a common identifier, and no such legal obstacles which cannot be overcome. Such a project is already underway, coordinated by CHESS of THL, chaired by Unto Häkkinen. EUROHOPE (European Health Care Outcomes, Performance and Efficiency) is an EU-funded project in seven European countries, namely Finland, Sweden, Norway, the Netherlands, Hungary, Italy, and Scotland, which will analyze utilizing administrative databases, among other disease, also stroke. The first results are expected to be available in the year 2012.

Still, it is the original purpose of this study that needs the most urgent attention. Large scale registries of vascular disease are generally believed to lead the way towards higher quality and lower costs in healthcare systems (*Ryan 2010*), although making hospital performance data public may not automatically lead to corrective measures and improvements in performance, as was shown in the Canadian EFFECT study on cardiac care (*Tu et al. 2009*). The annual reports of PERFECT Stroke, which currently are large sets of raw tables published on a website, should be made more user-friendly to hospital administration and decision makers. Graphical presentation of the data, combined with a commentary, is a first priority. To be more effective, actually implement change, and truly improve quality, specific quality indicators, such as the proportion of patients treated in stroke centers, with thrombolytic therapy, and with secondary prevention according to national guidelines, should be prioritized, set target levels for, and widely communicated. The reports should be made available faster. These are specific challenges for the PERFECT Stroke steering group, and the whole PERFECT project.

Also the PERFECT Stroke database could be improved. For epidemiological purposes, inclusion of patients who died before admission to hospitals, as retrieved from the CDR, could be useful, although there is little that can be done in the healthcare system for these patients. Still, the size of this group may partly reflect the success or failure of primary prevention. For health system research, burden to society, and to simply count the number of bed-days stroke patients consume annually, also recurrent cases could be included in the registry. Some sort of measures for stroke severity and functional recovery would be on the top of the wish list, but difficult to collect in a systematic way for the whole country. Complications and thrombolytic therapies should be coded more stringently, which could be promoted with educational campaigns.

Implications of the current study on practice are clear. Stroke patients should be treated only in stroke centers and with guideline secondary preventive medications. This is not currently the case in Finland or elsewhere and something should be done. The responsibility lays with the ~20 chief physicians of the neurology departments in our country to convince the administration and political decision makers, secure the resources, and make sure all patients are treated in adequately equipped units specialized in the care of stroke patients. This will save lives and prevent patients from ending up in institutional care which is truly expensive. Even if the initial hospital costs may increase with stroke center care, the total costs only do very little, while the survival of stroke patients and the quality of life of both patients and caregivers undoubtedly will improve.

7 SUMMARY AND CONCLUSIONS

To conclude, the PERFECT study has succeeded in forming a nationwide stroke database in Finland. With ~95% specificity and ~90% sensitivity for including all national stroke patients, 100% follow-up, and many meaningful measures on stroke care and outcome, the database should serve both clinicians and managers in the planning, implementation, evaluation, and improvement of care for stroke patients in Finland.

In this study, a decline in stroke incidence, case-fatality, and mortality over the years 1999 to 2008 were observed, continuing the trends seen since the 1970's in Finland. A natural explanation is from more patients being treated in evidence-based specialized stroke facilities and with guideline acute and secondary preventive medications. The success of primary prevention, steady improvement in the treatment of risk factors of stroke in the population, is likely to be as important.

Evidence for benefit from organized care of stroke patients has been around for twenty something year, but the trials were done in settings very different from current stroke centers. In this study it was shown for the first time that patients treated in state-of-the-art stroke centers fulfilling stringent quality criteria are more likely to be alive and avoid institutional care than patients treated elsewhere. These results suggest that stroke patients should be treated in sufficiently specialized and well-equipped centers, a level usually attained and attainable only by large hospitals.

The direct healthcare costs of individual stroke patients are significant, being on average ~20 000 € over the first year since stroke, and on average ~85 000 € over the whole remaining life-time after stroke. The expected survival of stroke patients is increasing, which will in the future further increase the lifetime costs of stroke patients, and the total share of stroke patients of the national healthcare expenditure, which is currently 7%, although only two thirds of these costs are directly related to the stroke.

While the trends in the quality of care and outcome of stroke patients in Finland have been positive, there is still much room for improvement, and by no means can we be satisfied with the current state. One third of stroke patients do not currently gain access to stroke centers, either due to geographical reasons, or due to local policies. This is unacceptable. Patients living in an institution before their stroke are unlikely to gain independence afterwards, but they represented only 6% of the patients in the present study. Those living at home may continue to do so if given a proper change at effective acute care and rehabilitation. Here we need to see a change in Finland. A second area in need of major improvement is the coverage and completeness of secondary prevention. Systems to continuously monitor success in risk factor control after stroke are missing, although national attempts have been made. Presently, we can only evaluate the purchases of medications after stroke, which are inadequate in half of ischemic stroke survivors. This needs to be improved, and is the responsibility of the neurologists in Finland.

Most of the data presented in this study has relevance in Finland. There are two messages for the international audience also. 1.) Modern stroke centers with an intensive and fully equipped service are effective, and should be made available for all stroke patients. 2.) It is possible, in a suitable setting with high-quality administrative registries and a common identifier, to avoid the huge workload and associated costs of setting up and hand-collecting the data of a conventional stroke registry, and still acquire a fairly comprehensive set of information on stroke care and outcome.

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Another register study, the Helsinki Stroke Thrombolysis Registry (HSTR), has positively influenced my development as a scholar and this thesis. From the HSTR project I learnt multivariable statistical methods and came to understand factors influencing stroke patient outcomes. The HSTR study was initially kicked off by Turgut and Make after I started to gather into one file a list of all the patients treated with thrombolysis, as such a list was needed for the PERFECT project. **Perttu J. Lindsberg** did compare such aspirations to ancient archeology at the time. A special thanks to **Jukka Putaala** and **Daniel Štrbian**, with whom it has been a special pleasure to write articles with. Together with the rest of the HSTR team, **Sari Atula**, **Satu Mustanoja**, **Tiina Sairanen**, **Marjaana Tiainen**, **Ville Artto**, **Sami Curtze**, **Lauri Soinne**, **Olli Häppölä**, **Katja Piironen**, **Kirsi Rantanen**, **Oili Salonen**, **Heli Silvennoinen**, **Ron Liebkind**, and **Janne Pitkaniemi** I have learned many lessons in scientific writing and group dynamics.

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Inkoo, June 2011

A handwritten signature in dark ink, appearing to be 'Atte Meretoja', with a long horizontal stroke extending to the right.

Atte Meretoja

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